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CARCINOMA SUBSEQUENT TO THE RADIOTHERAPEUTIC MENOPAUSE*

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IN THE routine follow-up examination of about 1,100 patients in whom an artificial menopause had been induced because of benign uterine bleeding, fibromyoma, or one of a few other benign conditions, there were noted 36 cancers in various parts of the body, 15 of which were of the uterus (9 in the corpus and 6 in the cervix). This may not appear to be a large number of cases in view of the fact that some of the patients were under observation for as long as twenty-five years. However, the data seemed sufficient to warrant a thorough statistical analysis. The results of this analysis showed that there was a slight excess of cancer other than uterine and a statistically significant excess of cancer of the uterus, particularly of the corpus, over the number that might be expected to occur among an equivalent group of the general population followed for the same length of time.

Similar series of patients have been reported and discussed by Werner,[1] Vogt,[2] Burnam,[3] Norris and Behney,[4] Schmitz,[5] Strachan,[6] Luker,[7] Costolow,[8] Scheffey[9] and Macfarlane.[10] The observed cases of carcinoma in the different series amounted to from 0.3 to 1.46 per cent of the patients originally treated by the artificial menopause. However, the validity of these percentages cannot be assessed generally because the number of patients followed is not stated. Furthermore, these percentages cannot be interpreted safely as incidence figures,

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since the duration of the follow-up is not given, except in the case of Burnham,[3] who found an incidence of 1.46 per cent for cancer of the uterus among 625 patients followed for ten or more years.

Since it is important to determine whether the threat of carcinoma is sufficient to influence the management of these benign cases, an accurate estimate of the probability of such a patient subsequently contracting carcinoma should be made. This has been made possible by the records of 1,108 patients of whom 958 were followed for an average of 6.7 years each, giving an aggregate experience of 6,402 person-years, which would seem entirely adequate for an extended statistical analysis.

TABLE I. LENGTH OF FOLLOW-UP OF PATIENTS IRRADIATED FOR BENIGN UTERINE CONDITIONS AND CARCINOMAS DEVELOPING DURING THIS FOLLOW-UP

AGE WHEN TREATED	DURATION OF FOLLOW-UP									TOTAL CASES WITH FOLLOW-UP	LENGTH OF FOLLOW-UP (YEARS)		NUMBER OF CARCINOMAS	
	0 YR.	UNDER 1 YR.	1-2 YR.	2-4 YR.	5-9 YR.	10-14 YR.	15-19 YR.	20-24 YR.	25-29 YR.		TOTAL	AVERAGE	ALL KINDS	UTERINE
Below 25	2	1	2	3	3	1	2	2	0	14	129.0	9.2		
25-29	3	3	0	3	5	4	0	1	0	16	122.0	7.6		
30-34	5	4	2	10	14	6	1	1	0	38	260.0	6.8	1	
35-39	24	9	14	25	44	17	5	4	1	119	860.5	7.2	2	
40-44	49	21	41	81	86	41	18	6	0	294	1,963.0	6.7	12	7
45-49	39	33	40	87	90	53	13	5	1	322	2,086.0	6.5	14	5
50-54	26	14	22	30	38	15	5	3	0	127	772.5	6.1	6	3
Over 55	2	1	2	8	11	4	0	2	0	28	209.0	7.5	1	
Total	150	86	123	247	291	141	44	24	2	958	6,402.0	6.68	36	15

TABLE II. CASES OF NONUTERINE CARCINOMA SUBSEQUENT TO RADIATION THERAPY FOR BENIGN UTERINE CONDITIONS

CASE NO.	SITE	AGE WHEN TREATED	YEARS AFTER TREATMENT WHEN CANCER OCCURRED	YEARS OF FOLLOW-UP
1	Ovary	49	9	10
2	Ovary	48	6/12	6/12
3	Stomach	49	9	10
4	Thyroid	39	1	5
5	Rectum	44	3/12	4/12
6	Rectum	35	8	8
7	Rectum	45	9	9
8	Bladder	40	20	20
9	Bladder	50	13	24
10	Breast	45	5	28
11	Breast	44	3	7
12	Breast	50	10	16
13	Breast	43	8	8
14	Breast	56	5	24
15	Breast	46	14	14
16	Breast	46	7/12	7/12
17	Breast	48	5	5
18	Breast	51	1	2
19	Sigmoid	44	10	12
20	Sigmoid	34	13	13

The fundamental data on which this study is based are given in Tables I, II, and III. Table I gives the distribution of the 1,108 patients with respect to age at entry into the study, and length of follow-up. It will be noted that practically all of the patients entered between the ages of 30 and 55 years. The subsequent analysis relates only to the 958 patients who were actually followed. While the 150 patients without follow-up may be a selected part ofthe whole,

TABLE III. TABULATION OF PRINCIPAL CLINICAL ASPECTS OF CASES OF UTERINE CARCINOMA SUBSEQUENT TO RADIATION FOR BENIGN CONDITIONS

		ORIGINAL TREATMENT				CARCINOMA					
CASE NO.	AGE (YR.)	INDICATIONS AND SIZE OF UTERUS	CURETTINGS BIOPSY	TREATMENT	ONSET OF AMENORRHEA	OCCURRED AFTER TREATMENT (YR.)	DURATION OF BLEEDING	OPER. FINDINGS	MICROSCOPIC	TREATMENT	RESULT
Cases of Carcinoma of Corpus											
1	43	Bleeding Ut. 4 mo.	Endometrium Normal	D. & C. Ra.	1 mo.	9	2 wk.	Extensive ca.	Adenoca.	Hyst. & X-ray	D. 2 yr. Ca.
2	46	Bleeding	0	X-ray		10	3 mo.		Adenoca.	Hyst.	D. 10 yr. Tbc.
3	51	Bleeding Ut. 6 wk.	Cyst. & Gl. Hyperplasia	D. & C. Ra.	2 mo.	4	3 wk.		Adenoca.	Hyst.	A.W. 9 yr.
4	48	Bleeding Ut. 2 mo.	Mod. Gl. Hyperplasia	D. & C. Ra.	Cont. 3 mo. X-ray	21	?		Adenoca.	Ra.	D. 1 yr. Ca.
5	40	Bleeding	Cyst. & Gl. Hyperplasia	D. & C. Plastic X-ray	1 mo.	9	?		Adenoca.	Hyst.	A.W. 6 yr.
6	50	Bleeding Ut. 2 mo.	0	X-ray	1 mo.	10	10 days		Adenoca.	Ra. & hyst.	A.W. 4 yr.
7	49	Bleeding Ut. 4 mo.	0 Cyst. & Gl.	X-ray	1 mo.	9	1 mo.		Adenoca.	Ra. & hyst.	A.W. 4 yr.
8	43	Bleeding	Hyperplasia	Plastic D. & C. X-ray	Immediate	2	1 mo.		Adenoca.	Ra. & hyst.	A.W. 5 yr.
9	49	Bleeding	?	D. & C. Ra.	Immediate	13	?		Adenosarcoma	Hyst.	D. 2 yr. Ca.
Cases of Carcinoma of Cervix											
10	44	Bleeding Ut. 5 mo.	Curettings none	X-ray	3 mo.	8	3 wk.	Endocervix	Adenoca.	D. & C. Ra.	D. 2 yr. Ca.
11	45	Bleeding	No curettings	D. & C. Ra.	Immediate	6	1 yr. & 2 wk.	Endocervix	Adenoca.	D. & C. Ra. X-ray	D. 4 yr. Ca.
12	41	Bleeding Ut. 3 mo.	Normal secretory	D. & C. Ra.	1 mo.	18	1 mo.	Cervix	Squamous	D. & C. Ra. X-ray	Alive with Ca. 9 mo.
13	40	Bleeding Ut. 2 mo.	Mod. gland. Hyperplasia	D. & C. Ra.	Immediate	12	6 mo.	Endocervix	Squamous	D. & C. Ra. X-ray	A.W. 4 yr.
14	51	Bleeding Ut. 4 mo.	Normal proliferative	D. & C. Ra.	Immediate	7	?	?	Squamous	?	D. 2 yr. Ca.
15	42	Bleeding	Normal proliferative	D. & C. Ra.	1 mo.	12	2 mo.	Endocervix	Squamous	D. & C. Ra. X-ray	A.W. 2 yr.

Key: Size of uterus is compared with the pregnant uterus. Cyst. = cystic; Gl. = glandular; D. & C. = dilatation and curettage; Cont. = continued; Hyst. = hysterectomy; D. = died; A. W. = alive and well.

such possible selection should not influence greatly the generality of the results, in view of the relatively small size of this group. Table I also gives the number of carcinomas developing among the patients according to their age at entry. The more detailed classification of the 36 carcinomas as to the site, age of the patient, and length of follow-up is given in Tables II and III.

Before undertaking the detailed analysis of the data given in Table I, we shall first present some preliminary calculations concerning the general population. In the first place, we may inquire as to the proportion of females in the general population between the ages of 30 and 55 who will survive to the age of 80. According to the annual mortality rates from all causes at the various ages prevailing among females in the United States in 1930, it may be deduced by the usual actuarial procedures[11] that some 26 to 31 per cent of women between the ages of 30 and 55 will survive to the age of 80.

Second, we may inquire as to the proportion of these females in the general population in the age group 30 to 55 who would contract cancer by the age of 80. This proportion can be determined by following through such a group of individuals, subjecting the survivors year after year to the appropriate annual incidence rates of cancer at the various ages. Since we do not know the annual incidence rates of cancer at the various ages, because cancer is not generally a reportable disease, we shall have to use the annual mortality rates, modifying these, if possible, to reflect incidence more clearly. For this purpose it was assumed that the incidence rate in any age group could be taken approximately as the mortality rate among individuals five years older. Thus the individuals between the ages of 35 and 40 are regarded as subjected to the risk expressed by the annual mortality rate pertaining to individuals between the ages of 40 and 45. As a result of this modification, our estimate of the probability of contracting cancer is about 20 per cent higher than it would be if death rates were employed directly as incidence rates. It might be argued that this modification assumes that a case of cancer survives some five years on the average. While this average may be exaggerated, any such exaggeration will leave a margin for the fact that not all cases of cancer terminate fatally. Applying the mortality rates, as given in Table IV[11-13] in the manner described above, to a group of females in the general population between the ages of 30 and 55 followed year by year until the age of 80, it follows that some 15 per cent will have had cancer by the age of 80, and some 2.8 per cent cancer of the uterus.

Thus, among our 958 patients, all of whom were essentially between 30 and 55 years, we might accordingly expect some 15 per cent, or 144, to develop cancer, and some 26, cancer of the uterus, if they were comparable to the general population and were all followed to the age of 80. However, since the 958 patients here studied were followed for only 6.7 years on the average and not until the age of 80, it is obvious that the numbers 144 and 26 cannot be used as the normal expectancy. We shall have to employ some modification of the above procedure in order to determine the number of cancers which would be expected among a group of 958 females in the general population distributed by age and followed up as are those of Table I.

TABLE IV. DEATH RATES PER 100,000 FEMALES FROM CANCER AND OTHER MALIGNANT TUMORS, AND FROM CANCER OF THE UTERUS, UNITED STATES, 1930

AGE (YEARS)	CANCER AND OTHER MALIGNANT TUMORS	CANCER OF UTERUS
25-29	13.8	5.1
30-34	32.0	12.7
35-39	58.4	21.0
40-44	113.3	40.7
45-49	172.1	54.2
50-54	249.2	69.6
55-59	356.2	87.2
60-64	458.7	92.4
65-69	595.5	102.0
70-74	803.4	114.7
75-79	948.2	110.8
80-84	1111.2	125.3

TABLE V. DETERMINATION OF FOLLOW-UP IN TERMS OF PERSON-YEARS FOR THE 294 PATIENTS ENTERING AT AGE 40, AND THE EXPECTED CASES OF CANCER

(1) AGE AT TREATMENT	(2) NUMBER REMAINING IN THE STUDY	(3) NUMBER WITHDRAWN FROM OBSERVATION	(4) PERSON-YEARS OF OBSERVATION IN THE AGE GROUP	(5) EXPECTED CASES* OF CANCER
40	294	21	283.5	0.5
41	273	41	252.5	0.4
42	232	81	574.5	1.0
45	151	86	540.0	1.4
50	65	41	222.5	0.8
55	24	18	75.0	0.3
60	6	6	15.0	0.1
65	0	0		
Total			1963.0	4.5

*Applying to column (4) the mortality rates of Table IV pertaining to persons in the age group older by 5 years.

We may illustrate the procedure employed by following through the calculations for the 294 patients entering in the 40 to 45 age group. As seen in Table I, these were followed for a total of 1,963 years or 6.7 years on the average. Each of the 1,963 years is the equivalent of one person followed for one year and represents a unit of exposure to the risk of contracting cancer expressed by the annual incidence rate. We shall follow the customary practice of denominating this unit a "person-year." In order to determine properly the number of cases of cancer to be expected among these 1,963 person-years, it is necessary to distribute them by age, since the risk of contracting cancer varies with age. The method of simultaneously calculating the exposure and distributing it by age is analogous to that utilized by insurance companies and is illustrated in Table V for these 294 patients. For simplicity, they are all regarded as entering the study at the age of 40 years. Beginning with 294 patients 40 years of age, we note from Table I that 21 have left the study before the end of the first year, so that there are only 273 remaining at the age of 41 years. Of these, 41 withdrew before the end of the second year, leaving 232 at 42 years of age, and so on, until there are no patients left by the age of 65 years. The number of person-years is then calculated for each age group. For example, in the 45 to 50 group, of the 151 present at the age of 45 years, 86 are lost from observation and only 65 remain by 50 years of age. These 65 must be credited

with 5 years of exposure each in this age group—that is, 325 person-years in all. The 86 lost from observation are assumed to be withdrawn uniformly throughout this period, being credited with 2½ years each, on the average, that is, 215 person-years in all. The total number of person-years between the ages 45 and 50 is thus 325 plus 215, or 540. The exposure in the remaining age groups was calculated similarly. Multiplying the person-years in each age group by the appropriate death rates modified as previously indicated, we obtain 4.5 as the expected number of cases of all cancers among the 294 patients, contrasted with the observed number of 12 cases. Similarly multiplying by the death rates for cancer of the uterus, we find 1.3 expected cases, as compared to the observed number of 7.

TABLE VI. AGE DISTRIBUTION OF 6,402 PERSON-YEARS ACCUMULATED BY 958 PATIENTS FOLLOWED UP FOR VARYING PERIODS AS GIVEN IN TABLE I

AGE	PERSON-YEARS
20-24	54.0
25-29	94.5
30-34	210.0
35-39	573.0
40-44	1,390.5
45-49	1,833.5
50-54	1,297.5
55-59	644.0
60-64	215.0
65-69	65.0
70-74	20.0
75-79	5.0
Total	6,402.0

By the same procedure as that just employed for the 294 patients entering at the age of 40 years, the exposure of each group of patients was calculated and distributed according to age. For this purpose, the 14 patients under the age of 25 years and the 28 patients over 55 years were regarded as entering at the ages of 20 and 55 years, respectively. The age distribution of the total 6,402 person-years, obtained by summing the various tables similar to Table V, is given in Table VI. Multiplying the person-years by the appropriate death rates, we find that there should be 17.4 cancers, of which 4.4 should be cancer of the uterus. The observed number of cancers, 36, of which 15 are of the uterus, is far in excess of the expected number, the difference being statistically significant. This seems largely accounted for by the excess of uterine cancers, which is very significant, the ratio of the observed cases to the normal expectancy being 3.4. In fact, the incidence of cancer other than uterine does not seem unduly large, the observed number being 21 and the expected 13. This will be discussed below in more detail.*

The observed and expected cases of cancer for each age group at entry into the study are separately portrayed in Table VII, showing that the excess is

*It should be noted that the follow-up data as given in Table I and as further shown in Table VI includes the follow-up on the 36 patients after they contracted cancer. It might properly be argued that this latter follow-up is biased. However, the follow-up on the 36 patients after contracting cancer is negligible, amounting to only 127 person-years, as may be observed from Tables II and III. Since this constitutes only 2 per cent of the total follow-up, the extra refinement of subtracting these 127 person-years in the appropriate age groups in Table VI was not deemed necessary.

TABLE VII. OBSERVED AND EXPECTED CASES OF CANCER BY AGE AT ENTRY OF PATIENT INTO THE STUDY

AGE		UNDER 25	25-29	30-34	35-39	40-44	45-49	50-54	OVER 55	TOTAL
All Cancer	Observed cases	0	0	1	2	12	14	6	1	36
	Expected cases	0.1	0.1	0.2	1.4	4.5	6.6	3.3	1.2	17.4
Uterine Cancer	Observed cases	0	0	0	0	7	5	3	0	15
	Expected cases	0.0	0.0	0.1	0.4	1.3	1.7	0.7	0.2	4.4

consistently present in all the age groups in which there was an appreciable number of patients.

We conclude from the statistical analysis that, in patients selected as were ours, subsequent to the radiotherapeutic menopause for excessive uterine bleeding, fibromyoma of the uterus, or for other benign conditions, carcinoma of the uterus occurs some 3.4 times as frequently as in the general population. Since some 2.8 per cent of women in the general population between the ages of 30 and 55 years will contract carcinoma of the uterus by the age of 80 years, we might conclude that 3.4 times 2.8 per cent, or 9.6 per cent, of the group here followed will be similarly afflicted.

There is not a corresponding excess of cancers in other organs. While 21 of these were observed instead of an expected 13, five were discovered within one year of the first observation and according to the prevailing custom would be considered coincident with and not subsequent to the original contact, leaving 16 which were properly subsequent to the original procedure, an excess statistically not significant. We shall discuss these cases no further except to point out with proper humility that a specialist treating women of this age group must accept the responsibility for a complete diagnosis before instituting any form of therapy. We shall hereafter confine our discussion to the uterine carcinomas.

While a statistical analysis has been justified in view of the mass of data, we must examine the reliability and validity of the original observations and of some of the assumptions made in the analysis.

The employment of the mortality rates as incidence rates is subject to two possible errors. The reliability of the mortality rates has been studied by MacDonald,[14] who finds an error of understatement in the reporting of carcinomas of some 6 per cent, the error being greatest for the inaccessible growths. That the error is greater than this is suggested by Pohlen and Emerson,[15] who, in a comparison of clinical diagnosis with autopsy findings, found that the clinical topographical and etiological diagnosis was correct in only 65 per cent of the cases of carcinoma of the corpus and in 86 per cent of the carcinomas of the cervix. In addition, since cancer is not generally a reportable disease, there are very little data from which to study its incidence. It was necessary, therefore, to employ mortality rates as a basis for calculation. Because of the high fatality rates, these have been assumed[16] to give a reasonably good picture of incidence also. Against this assumption, we know that a respectable number of patients treated for cancer of the uterus survive for five or more years. In New York State, where cancer has been a reportable disease since 1940, there were reported, in 1942, 1,330 new cases of cancer of the uterus,[17] while in that

same year only 905 deaths were recorded, giving an excess of living new cases over deaths of 47 per cent, more than double our correction of 20 per cent. The "new" cases, however, probably include cases which had existed prior to 1942 but were not reported and may not indicate the actual incidence. It is quite likely that our correction is a conservative one.

Regardless of the incidence figures used as a basis of calculation, the estimate 9.6 per cent already given as the probability of contracting cancer of the uterus by the age of 80 years among women similar to the ones here studied will be essentially correct. This is due to the fact that any change effected in the estimate of 2.8 per cent for the normal probability by the choice of different incidence rates would be accompanied by a compensatory change in the ratio 3.4 which the observed 15 cases of cancer of the uterus bear to the normal expectancy.

The question may be raised as to whether these cancers were truly "subsequent" to the original procedure or whether they were present at the original treatment and overlooked, remaining quiescent for a number of years and possibly even being inhibited by the sterilizing dose of radiation.* It is customary in considering cancer of the cervical stump to consider cases revealed within two years and by some, three years, as having been present when the hysterectomy was performed. Applying this rule to the six cases of cancer of the cervix here presented, all of them would be classified as "subsequent" since the shortest interval was six years.

Cancer of the corpus may lie quiescent for a longer time and the determination of whether or not it was coincident with the original treatment is more difficult. In the cases here reported the intervals were 2, 4, 9, 9, 9, 10, 10, 13, and 21 years, respectively. The patient with the two-year interval (Case 8, Table III) was treated at the age of 43 by a complete vaginal plastic. Because of moderately excessive menstruation she was given an x-ray menopause. The curettage performed by the "fractional" technique yielded normal appearing endometrium which was diagnosed microscopically as cystic and glandular hyperplasia. The periods stopped immediately. Two years later curettage for recurrent bleeding revealed a diffuse, apparently superficial adenocarcinoma. This case is entered as "subsequent" because it was handled throughout by one of us. The curettage was meticulous and if a carcinoma was overlooked, it was too small to be revealed in the curettings. Furthermore, the x-ray dose of 400 roentgens to the uterus is insufficient to affect an adenocarcinoma.

The patient with the four-year interval, Case 3, was treated by intrauterine radium (1,800 mg. hr.) for uterine bleeding from a slightly enlarged uterus. Curettage yielded a polyp and endometrium showing cystic and glandular hyperplasia. Four years later curettage for recurrent uterine bleeding yielded a single bit of tissue 4 mm. in diameter, an adenocarcinoma. The uterus removed six weeks after a dose of 2,400 mg. hr. of radium showed no carcinoma. There may have been a malignant transformation of a polyp. If so, it was not apparent in the original specimen.

*We are here concerned only with the question of the validity of the data and not with the important problem of proper diagnosis in these cases, which has been ably discussed by Scheffey.[3]

Three cases were treated by x-ray without a curettage; one because of active pulmonary tuberculosis and two for personal reasons on the part of the patient, the decision to forego the curettage being shared, however, by the physician. In the tuberculous patient, Case 2, slight vaginal bleeding persisted for a year and suggested some organic lesion. The carcinoma appeared after an interval of ten years. Bleeding in the other two women, Cases 6 and 7, ceased promptly. The carcinoma appeared after nine and ten years, respectively. While the long interval suggests that the carcinoma was not present originally, its appearance at any time emphasizes the responsibility undertaken by the physician when a diagnostic curettage is not performed.

Inhibition of a cancer by intrauterine radium seems unlikely in these cases except possibly in Case 3 in which the carcinoma appeared four years after the original treatment. Among cases treated in our clinic for frank carcinoma of the corpus by intrauterine radium in doses of from 2,400 to 8,000 mg. hr. combined with x-ray therapy, in only one case was there a local recurrence of the carcinoma after three years. Since the shortest interval in our series of cases was nine years, with the exception of the cases above described, it seems improbable that radium inhibited a carcinoma present at the original treatment.

Inhibition of the cancer by the application of the x-ray as given also seems unlikely to have occurred since the dose reaching the uterus was only 400 r., obviously insufficient to affect an adenocarcinoma.

In a study of other ways in which these patients might be selected, there was nothing discovered in age, parity, economic status, or the nature of our local or hospital population. Conditions so widespread as abnormal bleeding at the menopause and fibromyoma determine a fairly unselected group.

Among the carcinomas of the cervix, there was one in an Orthodox Jewess. This was, however, an adenocarcinoma of the endocervix which may minimize the factor of immunity which women of this race seem to have against carcinoma of the cervix.

Fibromyoma was present in 54 per cent of the whole group and in 54 per cent of those who suffered from uterine bleeding, a proportion close to that obtaining in the general population and apparently without significance.

To the question as to whether the radiation employed might be a contributing cause of the carcinoma, we shall only refer to extensive evidence in the literature[18] which indicates that radiation with techniques and dosages such as were employed in these cases is not a cause of carcinoma.

The only way in which these women differed widely from their fellows was that a very large proportion suffered from excessive uterine bleeding. As may be seen from Table VIII, this was present in 87.4 per cent of the cases; in 40 per cent the uterus was grossly normal and in 47.4 per cent myomatous. Bleeding was the symptom requiring treatment in all of the cases subsequently contracting carcinoma. This abnormal bleeding is decidedly out of line with the experience of women in general who are approaching the menopause, among whom only 13 per cent suffer from excessive bleeding, while the other 87 per cent either stop abruptly or taper off gradually.[19] There appears then in this group to be a definite correlation between bleeding prior to the menopause and the

subsequent appearance of carcinoma. This implies that there is some anatomic or physiologic factor which makes these uteri fertile ground for the subsequent neoplastic process.

TABLE VIII. INDICATIONS FOR RADIOTHERAPEUTIC MENOPAUSE IN 722 OF THE 958 REPORTED PATIENTS

INDICATION	NO. OF PATIENTS	PER CENT
Total Bleeding	631	87.4
Without fibromyoma		
Menstrual excess	117	16.2
Intermenstrual bleeding	172	23.8
With fibromyoma		
Menstrual excess	171	23.7
Intermenstrual bleeding	171	23.7
Fibromyoma without bleeding	58	8.0
Other*	33	4.6
TOTAL	722	100.0

*Cases of artificial menopause for dysmenorrhea, endometriosis, sterilization, and non-pelvic conditions (headache, epilepsy, tuberculosis, etc.)

TABLE IX. DISTRIBUTION BETWEEN CORPUS AND CERVIX OF CARCINOMA OF THE UTERUS SUBSEQUENT TO RADIATION FOR BENIGN CONDITIONS

SOURCE	CORPUS	CERVIX
Scheffey		
Collected	40	18
Personal	12	7
Burnam	5	3
Sloane Hospital		
This study	9	6
First treated elsewhere	5	1
Total	71	35

This impression is strengthened by the unusually high proportion of carcinomas of the corpus of which there were nine as against 6 of the cervix, a proportion which is in agreement with that reported by other authors. In Table IX we have combined the cases collected and those personally reported by Scheffey,[9] those of Burnam,[20] and those of this study, together with 6 further cases observed by us but having had their radiotherapeutic menopause elsewhere. There are 106 cases of carcinoma of the uterus, of which 71 were in the corpus and 35 in the cervix, a ratio of 2 of the corpus to 1 of the cervix, a ratio six times as great as that existing in our clinic, which is 1 of corpus to 3 of cervix and fourteen times as great as the rate usually accepted (1 corpus to 7 cervix).[21, 22] Objection may be made that the normal ratio should be that for carcinomas occurring at the same ages at which they occurred in our series, where the average age was 55.1 for the cervix cases and 56.2 for those of the corpus. The ratio of corpus to cervix in our clinic at these ages is as 1 to 2, making the ratio in the 106 cases here reported four times as great. By whatever calculation, there is a significant increase in the proportion of corpus carcinoma.

Another interesting finding is an apparently high incidence of endometrial hyperplasia in the uteri which subsequently contracted carcinoma. Five of the 6 specimens examined showed, at the original curettage, cystic and glandular hyperplasia, while this was found in only one-third of the specimens taken

from the whole group of 958 patients. This observation agrees with that of Taylor[23] and is worthy of further study.

Still another unusual finding is the high incidence of endocervical carcinoma, 4 being in this region and only 2 on the portio. Of the 4 endocervical carcinomas, 2 are adenocarcinomas.

We conclude, then, that the high incidence of cancer of the uterus is largely due to the excess of carcinoma of the endometrium, that these carcinomas have occurred in endometria which bled excessively before the menopause and showed a higher incidence of hyperplasia. The nature of the processes or stimuli which brought about this combination of circumstances is food for interesting speculation and further study, but is beyond the scope of this paper.

The clinical application of these observations will depend on how seriously these figures are taken. Assuming that more extended studies will confirm our estimate that 9.6 per cent of women 30 to 55 years of age, requiring treatment for excessive uterine bleeding, etc., will sooner or later contract carcinoma of the uterus, we must decide whether this threat is sufficient to warrant a prophylactic complete hysterectomy, a procedure necessary to afford complete protection from subsequent carcinoma. In the cases in which hysterectomy is required because of the large size or of changes in a myoma, pedunculated submucous fibromyoma, coincident adnexal disease, undesirability of the menopause, etc., one need only to decide whether to perform a partial or complete hysterectomy. In the cases which would be proper subjects for an artificial menopause, the choice will lie between a simple procedure and a major operation. Following a sterilizing dose of radiation, bleeding will be controlled in 98 per cent of the cases and the myomatous mass will shrink satisfactorily in 95 per cent.[24] The procedure entails no mortality and little disability. The mortality from complete hysterectomy varies greatly in different clinics and is usually in inverse proportion to the number of operations performed, varying from 0.7 per cent[25] up to 6 per cent. When performed on uteri which would be proper subjects for an artificial menopause, it should present little technical difficulty and should be accompanied by the least danger. Nevertheless, in the past, dangers of prophylactic hysterectomy would have made such a routine practice unwise. In the future, improvements in the management of shock, hemorrhage, infection and thrombosis, and an elevation of the general level of surgical efficiency, should so lower the dangers of complete hysterectomy that it would be small compared with the threat of subsequent carcinoma. With this prospect, on the one hand, of lowering the operative risk and, on the other, of an increase in the already large number of carcinomas due to a still further increase in the proportion of people at the older ages, the element of prophylaxis should receive serious consideration in planning the treatment of a woman suffering from abnormal uterine bleeding.

Conclusions

1. Among 958 patients treated for benign uterine bleeding by the radiotherapeutic menopause and followed for 6.7 years each, on the average, there subsequently occurred 15 carcinomas of the uterus. Based on modified mor-

tality statistics, the same number of women in the general population during the same length of time should contract 4.4 carcinomas of the uterus. The observed number of cases is therefore 3.4 times as large as the number expected.

2. Two and eight-tenths per cent of women in the general population between the ages of 30 and 55 years contract cancer of the uterus before reaching the age of 80. Applying the above ratio of 3.4 we find that 9.6 per cent of women suffering from uterine bleeding prior to the menopause would contract the disease.

3. Of 15 cases, 9 were of the corpus and 6 of the cervix. This abnormal preponderance of carcinoma of the corpus is in agreement with that present in other reported cases in which the ratio is two of corpus to one of cervix. This ratio of corpus to cervix is six times that obtaining in our clinic.

4. It is inferred that the endometria of uteri which bleed abnormally prior to the menopause are predisposed to the subsequent development of carcinoma of the corpus.

5. Prophylaxis against carcinoma of the uterus should be an important factor in a plan of treatment for uterine bleeding prior to the menopause.

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THE VALUE OF PHYSIOLOGIC SUBSTRATES IN SPERM MIGRATION IN SELECTED CASES OF HUMAN INFERTILITY

Observations on a Series of 106 Patients

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THE reproductive process of man is indeed complicated in comparison with other species. As the processes of living become more specialized, survival of the species depends not so much upon being the "fittest," as upon the proper and efficient coordination of the intricate mechanism of reproduction and its complex psychological and economic elements.

In the mosaic of the intricate physiologic patterns and processes so essential to this biologic symmetry in fruitful reproduction, one can evaluate many of those factors requisite to the attainment of such an orderly physiologic progression in the reproductive organs of each sex. Much attention is paid to the major facets. The medical literature is replete with considerations of patency and nonpatency of the oviducts, congenital malformations, anovulation, so-called hostile cervical secretions, endocrinal imbalances, and other aspects which contribute to human infertility and sterility. There has been little stress laid upon the importance of other physiological variants which play vital roles in the complex process of human reproduction. Other problems to be considered with serious attention include the mechanisms of copulation, the biochemistry of the lower genital secretions in each sex, biochemistry of the ejaculate as related to the metabolism of its living cells, and the progressive continuity of fluid pathways for sperm migration. The alterations in vaginal flora also should receive consideration in all patients being studied for infertility.

The author wishes to present in this paper his experience with two of these problems, a consideration of the fluid pathways in the female for sperm migration and their influence upon sperm motility. In certain cases, selective in the sense that the major organic obstacles to fruitful impregnation are absent, it is possible that these minor physiologic and biochemical imbalances assume a major responsibility for continued infertility unless they are corrected. In a series of 106 barren couples studied, with these probabilities in mind, it was possible to obtain 29 successful impregnations wherein the treatment introduced was only the addition of a precoital physiologic substrate to insure a proper fluid pathway continuity which would meet the metabolic requirements of spermatozoa during their migration.

Animal Husbandry Experience With Physiologic Substrates and Spermatozoa

Prior to a discussion of this series, it was thought advisable to review some of the valuable data on animal infertility. Marshall,[1] thirty-five years ago,

observed the chemical differences which exist between the spermatozoa of the different species and orders did not show any connection with the zoological relationship.

Baker,[2] 1930, was among the first to use a buffered glucose saline fluid for keeping mammalian sperm in an active state at body temperature. Ivanov,[3] 1931, was the first to point out that motility in dog spermatozoa was little correlated to states of anaerobiosis except that greater concentrations of sperm under anaerobic conditions displayed an earlier loss of motility. Today this can be explained by a greater number of spermatozoa utilizing the available glucose in the process of anaerobic glycolysis. Hyme,[4] 1932, prolonged the motility of guinea pig sperm in an isotonic Ringer-glucose substratum.

Redenz,[5] 1933, related the modern view on cleavage metabolism of glucose to mammalian spermatozoa in relation to their motility. Bernshtein[6] observed that while nutrient substances in the substrate increase the motility, his solutions did not cause an increase in the survival time of the sperm. In a later paper, however, Bernshtein[7] did note that while the semen is outside the body, the glucose concentration of the fluid falls, but that of the spermatozoa remains relatively constant. Bernshtein and Slovachotov[8] reported, 1933, that fresh ejaculates of the bull *and man* contain about 40 mg. per cent of lactic acid which increases in the semen kept outside the body. They found the motility of the spermatozoa gradually decreases, but *its complete cessation occurs at different lactic acid levels.*

Ivanov[9] found, 1936, that the respiratory quotient of sheep spermatozoa approached unity in the presence of glucose and departed from unity in the absence of sugar. He[10] reported, in the same year, that the respiratory quotient of sheep spermatozoa in Ringer's solution alone was considerably less than unity and that the oxidation of lactic acid did not play any significant role in the respiration of spermatozoa in saline media.

Lloyd[11] and Anderson[12] independently pointed out the additional value of buffering animal sperm dilutors. The former found a pH of 7.5 isotonic glucose-saline dilutor to give more satisfactory clinical results, while Anderson obtained his optimum results with the glucose-saline isotonic substrate at a pH of 7.6. It seems significant that each author arrived at practically the same pH and considered the importance of isotonic solutions.

Warbutton, McKenzie, Berliner, and Andrews,[13] at the Thirtieth Annual Meeting of the American Society of Animal Production, 1937, were among the first to consider the relationship of pH along the entire course of the genital canal to sperm motility. They made pH determinations on the contents of the tubes, uterine horns, cervix, and vagina of inseminated ewes. They showed pH differences of as much as 0.8 unit for the two tubes and 0.4 unit for the two uterine horns of the same animal. The cervix was usually the most acid region, pH 6.1 to 7.6, and sperm remained normal there longer than in the rest of the genital tract. It was observed that the acidity developed in relation to the disappearance of the sperm. It must be recalled, however, that the ram has a more adaptable copulative mechanism to insure the deposit of sperm into the favorable cervical environment.

Phillips,[14] 1939, reported a case of bovine impregnation from bull semen after preservation in an egg yolk buffer solution at a pH of 6.7 for as long as 100 hours. His evidence includes documented records of pregnancy. Milovanov,[15] 1938, described an unique and very successful way to artificially inseminate farm animals with gelatinized sperm. Considerable care is taken with the insertion of these capsules into the more favorable cervical and uterine substrate.

Webster,[16] 1939, in his investigations on sheep semen found the seminal plasma had a high content of glucose, while the acid drift was associated with degradation of the glucose to lactic acid. It is not improbable that variable quantities of seminal glucose in different animal semen bears a reasonable correlation to the survival times. Telesforo[17] observed that there existed variable time limits for storage of semen: for cattle, semen from 50 to 120 hours; sheep, 75 to 120 hours; horse, 12 to 24 hours; and for the pig, 1 to 2 hours.

Davis and Williams,[18] 1939, studied variations in pH of the bull semen following repeated ejaculations. They observed that the average pH of the first ejaculate was 6.85; the

second, 7.23; and a third ejaculate, 7.21. They noted a significant correlation between the concentration of spermatozoa per cubic millimeter and the pH; the higher the concentration the lower was the pH. Comstock,[19] 1939, observed that glycolysis decreased as sperm aged. Smith and Asdell,[20] 1940, reported that the buffering capacity of semen decreases with age of the bull sperm. Stallion sperm loses its motility rapidly at any pH below 4.7 to 4.6.[21] Stallion semen possesses much less glucose content than other animal semen.

Lardy and Phillips,[22] 1941, point out that there is an active succinic acid dehydrogenase present in spermatozoa. Although glycolytic and oxidative processes probably furnish energy for motility under normal conditions, if both of these are blocked simultaneously, spermatozoa still can retain motility for considerable periods of time. Moore and Mayer,[23] 1941, observed an extremely variable sugar content in ram semen and conclude that the loss of mobility of the spermatozoa and sugar loss were often coincdent.

Dougherty and Ewalt,[24] 1941, in a study of 645 semen samples from 104 bulls, observed little correlation between the laboratory findings and breeding efficiency of the bulls, save for those conclusions which demonstrated a positive correlation between pH changes of semen in the first few hours and the motility and viability of spermatozoa. Swanson and Herman[25] determined that the factor most indicative of a bull's fertility was the length of time vigorous motility was maintained. Knoop,[26] 1941, was able to maintain cell life in bull sperm for 16 to 35 days using one buffered gelatin-egg yolk diluent, and 14 to 38 days with an egg yolk-buffered salt diluent.

Henle and Zittle,[27] 1942, demonstrated that differences in the maturity of bull spermatozoa played a role in oxygen consumption, seminal spermatozoa showing a lower rate than epididymal cells.

Lardy and Phillips,[28] 1943, report significant metabolic changes in bull, cock, and rabbit spermatozoa after varying certain electrolytes in their substrates. Varying the phosphate ions affected the glycolysis and motility of sperm in the presence of glucose. These processes were greatly depressed in the absence of the phosphate. The omission of magnesium ions from the medium depressed cellular respiration. Manganese and calcium ions affected motility, glycolysis, and respiration adversely. At least 0.005 mg. of potassium was necessary for the maintenance of optimum motility, while this and even higher concentrations stimulated respiration and glycolysis. We see in this excellent observation the tremendous importance of a balanced physiologic substrate to sperm metabolism. In a later paper these authors,[29] 1944, in discussing metabolism of bull spermatozoa concluded that phospholipids were evidently the source of intracellular reserve energy of spermatozoa. This energy is obtained by oxidative processes, and sperm *preferentially* obtain the energy for motility from the glycolysis of glucose or other glycolyzable sugar.

Green,[30] 1940, in a study on the chemistry and cytology of the sperm membrane of sheep characterized it as an albuminoid with the material remaining after extraction high in nitrogen content. Trypsin did not attack it and only slight action was noted with pepsin. This author suggests the use of acetocarmine stain and dark-field illumination in the evaluation of sperm quality in this species.

Day,[31] 1940, considers that stallion sperm fertilizability appears to depend on the total number of active sperm while the small number of abnormal sperm had no bearing on fertility.

Frank, Smith, and Eichom,[32] 1941, using a bull sperm diluent of embryonic tissue extract (10- to 13-day-old chick embryos) were able to prolong the life of the sperm remarkably. They report sperm viability for 22 to 46 days and observe that the fertilizing power of semen was not apparently altered.

Min-Chueh Chang,[33] 1942, implanted stilbestrol tablets in rams and followed this procedure with daily injections of 15 mg. of stilbestrol dipropionate for 31 days. Sperm production increased 7 to 9 days after the implantation, in proportion to the dosage. The effect lasted five days. Fertility was proved by artificial insemination tests. There was no effect on sex drive, sperm morphology, or quality of spermatozoa, although a strong tendency to sperm agglutination was noted after treatment.

It is unfortunate the excellent work of Hammond,[34] in 1927, upon the vaginal discharges of the cow have not been brought up to date. Up to this period, however, those histologic and cytologic observations summarize much more fundamental data on the lower generative tract than is available in any other modern single source. He considers the physical properties of mucus from the vagina to the uterus in great detail. Some day this wider approach may be considered in human fertility.

The animal husbandry aspects emphasize the value of physiologic substrate[3] to sperm motility, sperm migration, and correlative biochemical factors present in the substrate along the genital canals of each sex. The investigators in the animal husbandry field of infertility have demonstrated rather conclusively the equal importance of considering the biochemistry of these genital secretions to sperm as biologic tissue, as compared to the clinical specialists in gynecology who overestimate the primary organic obstacles to the neglect of these basic biochemical and cytologic factors.

Experience With Physiological Substrates and Human Sperm

The modern study of human spermatozoal metabolism is relatively recent. The application of fundamental observations from studies on animal spermatozoa to the field of human fertility or infertility was tremendously sporadic in nature until the last half decade. The medical literature, aside from intermittent and unapplied biochemical observations arrived at largely through the curiosity of a few lone workers, was almost as barren of therapeutic considerations of these factors as could be possible.

MacLeod,[35] 1939, repeating earlier investigators'[1-5] animal studies on sperm, using human specimens, came to the same conclusions, that human spermatozoal metabolism was almost exclusively a process of anaerobic glycolysis. He observed that maximum motility of human sperm suspended in Ringer-glucose solution was maintained for over three hours under anaerobic conditions, but decreased markedly in the same period in the presence of air or pure oxygen. In a later paper MacLeod[36] noted that, while the sperm glycolysis remained relatively constant from specimen to specimen, *large differences were found from individual to individual.* When the respiration of human spermatozoa was studied[37] in Ringer-phosphate media without glucose it was of such small magnitude that its existence was doubtful.

Zagami,[37] 1939, reported at length upon the chemical composition and physiochemical properties of seminal fluid. He discusses the density, pH, relative viscosity, surface tension, and other properties in his comparisons of the seminal fluid of man, dog, rabbit, and the cock.

Shettles,[38] 1940, observed that the rate of respiration of human spermatozoa varies inversely with the age of the specimen and directly with the number of cells per unit volume. Shettles was the first to record that human spermatozoa remained most active for several hours in pure nitrogen, nitrous oxide, helium, and in air reduced to a very low pressure. He observed that carbon dioxide in excess produces complete immobility within a few minutes and the motility can be restored when this gas is replaced by nitrogen, air, or oxygen. He was able to revive some human sperm from very low temperatures and have them remain active for several hours.

Zeller and Joel,[39] 1941, demonstrated that in human sperm cholinesterase and diamine oxidase occurred only in the plasma and not in the spermatozoa. The latter is derived principally from the seminal vesicles. These writers showed that compounds which react with the carbonyl group can decrease the motility of spermatozoa in low concentrations and increase motility in higher concentrations.

MacLeod,[40] 1943, using human cells, arrived at the same conclusions that Lardy and Phillips[22] reported on the bull spermatozoa. He found that succinic acid was oxidized but this reaction was not coupled with motility.

Ross, Miller, and Kurzrok,[41] 1941, found that sperm from men who were definitely fertile, probably fertile, and suspected of impaired fertility, all utilized glucose aerobically

in Ringer-carbonate media, in human follicular fluid and in semen. It is noteworthy to mention that, while these authors state they could determine no significant quantitative changes among the three groups of men, they did report that lesser quantitities of oxygen were consumed by three specimens from men probably infertile.

MacLeod,[42] 1941, in a study on the effect of certain substrates upon the metabolism and motility of human spermatozoa noted that deprivation of sugar at 38° C. caused failure of motility within two to four hours. These sperm could be revived again upon the addition of glucose *if* the spermatozoa had not been exposed to oxygen during the period of deprivation or if they had not been inert longer than thirty minutes. In this paper MacLeod discussed the possible application of these time relationships to the behavior of human spermatozoa in the male and female genital tracts. MacLeod and Hotchkiss[43] observed that 75 per cent of the human spermatozoa are found in the first 40 per cent of the normal ejaculate while the last portion of the split-ejaculate contained a higher concentration of glucose.

Hoagland and Pincus,[44] 1942, were able to report the revival of human and animal sperm after immersion in liquid nitrogen if they were later rapidly warmed to 35° C. by plunging them into a suitable and balanced isotonic medium.

The Clinical Use of a Precoital Physiologic Substrate in Human Infertility

Recently, MacLeod and Hotchkiss,[45] aware of the possible role of the isotonic media to the metabolism and motility of the human spermatozoa, utilized these biochemical principles in cervical applications in selected cases of human infertility. They reported 12 pregnancies in cases of long-standing infertility in which a precoital irrigation of the vagina with a balanced salt solution containing a high percentage of glucose was used. In the past three years 106 couples, exhibiting no obstructive pathology to sperm migration in the female partner and refractive to other routine antisterility therapy in one or both partners, were selected for clinical trial. In all instances, the sperm studies, endocervical studies, tubal insufflation or hysterosalpingography, and endometrial biopsies had been made.

The female partner was asked to record daily the basal body temperature readings. She was advised to add the carefully weighed solid salts of a Ringer-glucose mixture* to an exact amount of tap water. During her relatively fertile period, as determined from her individual basal body temperature chart, the patient preceded intercourse with a vaginal irrigation, using this balanced isotonic substrate as the solution. Care was taken to insure a retention of several cubic centimeters of this solution in the vaginal canal and intercourse followed soon after. In two successful cases the Ringer-glucose solution was used prior to artificial insemination. In 27 other cases the women were found pregnant between one and seven months after such simple treatment. Twelve cases, 40 per cent, conceived within the first fertile period in which the artificial substrate was added as a precoital irrigation. *In 19 cases the Huhner test was found positive after use of a precoital sugar douche wherein previous Huhner tests, without the use of the glucose substrate, were found negative.*

A survey of Table I will reveal the summarized individual observations of the 29 cases to successfully conceive following the use of a precoital Ringer-glucose irrigation. The period of infertility had varied between one and twelve years. The age of the patients ranged between 23 and 44 years.

*The Ringer-glucose salts used to prepare the isotonic substrates can be obtained under the commercial name of Nutri-Sal from Ortho Products, Inc., Linden, New Jersey.

TABLE I

CASE	AGE (YEARS)	LENGTH OF MARRIAGE (YEARS	LENGTH OF STERILITY (YEARS)	FACTOR OF STERILITY	HUHNER TEST BEFORE RINGER-GLUCOSE	HUHNER TEST AFTER RINGER-GLUCOSE	KURZROK-MILLER TEST	CONCEPTION FOLLOWING USE OF RINGER-GLUCOSE (MONTHS)
767	44	4½	4½	Negative Huhner	0	+	+	5
924	34	7½	6½	Oligospermia	0	Not done		1
970	30	3	1	Negative Huhner; cervicitis	0	Not done		1
624	30	4	1	Conical cervix; oligospermia	0	+	+	5
761	26	5	2½	Cervicitis; negative Huhner	0	Not done		1
772	36	14	3	Cervicitis	0	+		3 (aborted at 10 weeks)
C.M.	24	3	1⅛	Oligospermia	0	+		3
520	31	12	12	After 9 monthly attempts of artificial insemination with no success advised use of Ringer-glucose prior to insemination	Not done	Not done		1
280	28	6	6	Oligospermia	0	+		2
326	29	5	5	Oligospermia	0	Not done		2
770	39	1½	1½	Oligospermia	0	+	+	3
698	32	1½	1½	Oligospermia	0	Not done		1
871	23	3½	2¾	Negative Huhner	0	+		2
273	35	8	1	Negative Huhner; oligospermia	0	+		2nd pregnancy following vaso-epididymal anastomosis
817	34	8	6	Oligospermia	0	+		4
771	35	10	1½	Cervicitis	0	+	Negative	5
850	38	5	5	Oligospermia	0	+	Negative	7 (aborted at 2 months)
575	30	9	9	Negative Huhner	0	+		2
815	25	4½	2	Negative Huhner with trichomonas	0	+		3
E.P.	27	2	2	Cervicitis; oligospermia	Not done	Not done		1
378	29	3	2	Negative Huhner	0	Not done	+	1
424	33	9 (1 previous pregnancy 8 years)	4	Negative Huhner	0	Not done	+	2
504	31	8	8	After 5 monthly attempts of artificial insemination with no success, was advised to use Ringer-glucose prior to insemination	Not done	Not done		1
873	26	2½	1½	Oligospermia	0	+	Negative	1
845	29	4	3	Oligospermia; thick cervical plug	0	+	+	1
876	27	5	5	Oligospermia	0	+	+	4
852	32	8½	2	Negative Huhner	0	+	+	1
724	28	6	3	Cervicitis	0	+	Negative	1; ectopic pregnancy
894	32	7	5	Cervicitis	0	+	Negative	2

There were 76 other cases having cervicitis and/or oligospermia with negative Huhner tests in which a Ringer-glucose douche was advised and used, with no success.

All of the Huhner tests were done at or near ovulation time. Repeat examinations were usually made either in 48 hours, or the following month.

Most cases used Ringer-glucose solution during the "fertile period," as recorded by basal body temperatures.

Many of the successful cases had other examinations, performed prior to the use of Ringer-glucose solution, such as the study of endocervical secretions, tubal insufflation, hysterosalpingography, and endometrial biopsy.

There occurred four fetal losses, by sponatneous abortion in three cases and ectopic pregnancy in one case, giving a fetal loss of 13.4 per cent or about equal to the average fetal loss encountered in conceptions following normal copulation.

The important consideration is that among 106 barren couples 29 women (28.3 per cent) were able to conceive following no other therapy than the simple use of a precoital Ringer-glucose irrigation used at the individual "fertile period" as determined by the use of basal body temperature graphic records. In all instances, previous and more time-consuming and expensive infertility therapy of both or one partner had failed. One cannot escape the conclusion that this success was realized largely because of our attempt to capitalize upon known biochemical observations already extant in animal husbandry and the preclinical medical writings. The success again illustrates the rewards of simplicity in therapy when once the basic truths are available for in vivo application.

Discussion

When one reflects seriously about the purposes behind copulation other than the recognized need to attract the opposite sex to the other partner, there seem to exist other specific physiologic functions in the copulative mechanisms. During coition there is an admixture of vestibular gland secretions, cellular debris, cervical mucus, vaginal exudate, smegma from both individuals, Cowper gland secretions, reflux urinary droplets, bacterial flora from each partner's lower genital tract, in addition to the ultimate male ejaculate arriving at the orgasm. Is it amiss to compare the inthrust and outthrust of the male phallus in the copulative act to a biologic pestle thoroughly mixing the surface secretions in the receptive vaginal mortar to insure a uniformity of a physiologic substrate from these biochemical components possessing variable physical properties? The timing of the male orgasm to occur at the termination of this biologic act would seem to represent the most favorable moment when the surface secretions, so essential to maintenance of metabolism and sperm migration, were most favorably mixed to assure favorable deposition of the male cells. The female orgasm frequently induces early sleep, thus obviating increased chances of disturbing these biochemical relationships and conditions prepared during copulation for the most favorable sperm reception.

The vaginal precoital pH range is 3.4 to 5.0, while in the postcoital examination we find a pH range of 4.4 to 6.2 in the normal canal and a postcoital range of 6.0 to 7.4 in women exhibiting amenorrhea in prepubertal and menopausal ages.[47] The pH of the cervix ranges between 8.0 and 9.0 both precoitally and postcoitally. *The significant changes in pH occur in the vaginal canal and the seminal pool.* These findings seem to corroborate our previous considerations anent the function of copulative mechanics; i.e., there is a definite purpose in the phallic mixing of male and female secretions to insure receptive surface substrates. Because of these findings the writer cannot agree with Greenhill[47] that the pH plays little or no part in sperm metabolism although it must be considered but one facet of the biochemistry in the fluid pathway for sperm seeking cervical and uterotubal ingress.

It does not appear improbable that the use of a Ringer-glucose precoital irrigation, at the most favorable period, accomplishes several real contributions toward increasing the possibilities for sperm migration by furnishing additional sugar and isotonic electrolytes for stimulation of cellular metabolism and motility, through promotion of a propitious pH of the mixture of the vaginal secretions, by altering the viscosity of both the distal cervical mucus and the male ejaculate in the presence of a favorable isotonic substrate, and by providing a less abrupt metabolic shock for the spermatozoa.

When one considers the manifold aspects which can alter the surface substrates and glucose levels of the semen in the vaginal secretions, it becomes more obvious that Ringer-glucose isotonic solution used as a precoital irrigation does merit a definite place in the armamentarium of the physician confronted with infertility problems.

Summary

Evidence is cited to indicate the importance of physiologic isofonic substrates to sperm metabolism and motility.

The application of these important animal husbandry and preclinical laboratory observations to the relief of human infertility, in carefully selected cases, is discussed. Among 106 such couples, giving a history of 1 to 14 barren years, Ringer-glucose isotonic solution was used precoitally as a vaginal irrigation, and the author is able to report 29 successful conceptions, a salvage of 28.3 per cent from this group of infertile patients.

This procedure, because of its simplicity in application, is worthy of extended clinical trial and is recommended in those cases of infertility exhibiting no obstructive organic pathology.

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POSTMENOPAUSAL ENDOMETRIUM AND ITS RELATION TO ADENOCARCINOMA OF THE CORPUS UTERI

A Study of 236 Cases*

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THE question of whether a given malignant neoplasm passes through a premalignant phase often is raised and hence should be considered as fundamental. Since the problem obviously is closely allied with early diagnosis and treatment, the question is not purely academic but practical as well. Thus, if a premalignant phase definitely could be established, physicians could strive to diagnose the condition during this period and eradicate it, with consequent prevention of the malignant neoplasm. The foregoing fundamental question prompted a study of the postmenopausal endometrium and its relation to adenocarcinoma of the corpus uteri.

In the many previous studies that have been reported in the literature, diversity of opinion has arisen because of lack of preciseness in the use of terms such as "hyperplasia" and "hypertrophy" and because of attempts to give these histologic terms a clinical significance. The definition of the term "hypertrophy," according to Boyd,[1, 2] is an increase in the size of individual cells or fibers as a result of which the organ may become enlarged. Enlargement of an organ from any other cause should not be called hypertrophy. The term "hyperplasia" means an increase in the number of cells of a part. Its limits are less well defined than those of hypertrophy and it might gradually merge into the process of neoplasia.

The term "endometrial hypertrophy" was introduced by Cullen[3] in 1900 and later was adopted by Novak and others. In 1915, Novak[4] recognized the difference between so-called hypertrophy and what he thought to be another entity, namely, hyperplasia, and thus he introduced into the literature the term "endometrial hyperplasia." This term immediately acquired a clinical connotation which largely supplanted any precise histologic definition which it originally might have had. The microscopic picture usually denoted as endometrial hyperplasia is one of great glandular proliferation with complete absence of luteinic change and decidual reaction. The glands may be lined by several layers of cells and there may be some degree of invasion of the muscular wall. The deeper glands may show cystic dilatation, giving what Novak called the "Swiss-cheese

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appearance." The stroma is abundant, and the superficial layers may show patchy necrosis, hemorrhage, and infiltration with inflammatory cells. Follicular cysts of considerable size may be present in one ovary; the other ovary may be shrunken and sclerotic. There is a notable absence of corpus luteum.

Herrell and Broders[5] expressed the opinion that such terms as "endometrial hypertrophy" and "endometrial hyperplasia" convey little information with respect to the histologic appearance of the endometrium. They maintained that the differentiative phases in the menstrual cycle repeatedly have been confused with hypertrophy. These investigators also stated that they preferred the term "cystic endometrium" to the term "Swiss-cheese hyperplasia" or "cystic hyperplasia." They pointed out that cystic endometrium has been diagnosed by some as hypertrophied endometrium and expressed the opinion that this cystic condition accompanies clinical ovarian failure or the approaching menopause rather than hyperplasia. Furthermore, they said that sudden withdrawal or failure of ovarian tissue is accompanied by true atrophy which consists of loose stroma with a few nonfunctioning basal and subbasal glands.

The presence of subbasal glands, as described by Herrell and Broders, has been said by various investigators to be pathognomonic of the menopausal age and even pathognomonic of hyperplasia. These workers have claimed that this process is identical with external adenomyosis. Herrell and Broders, however, observed the presence of these structures during all phases of the menstrual cycle, and also at all ages from intrauterine life (endometrium of a fetus, 30 weeks of age) to twenty years past the menopause.

In this paper such terms as "endometrial hypertrophy," "endometrial hyperplasia," "cystic hyperplasia," and "Swiss-cheese hyperplasia" will not be used except as necessary in review of the literature.

Review of Literature

The histology of the normally and abnormally functioning adult endometrium has been thoroughly studied in recent years. The alterations which occur during the normal menstrual cycle and the changes produced by different types and degrees of ovarian failure have been described by many writers. The postmenopausal endometrium has received little attention, however, and it usually is assumed that after the menopause the endometrium merely becomes atrophic. Most textbooks of pathology, for example, allude to the postmenopausal endometrium as being atrophic. Undoubtedly every pathologist has seen endometrium removed years after the menopause which histologically resembled that removed during the period of active menstrual function. A careful search of the literature, however, revealed only a few reported studies concerning the frequency of occurrence of this type of endometrium.

In 1941, Novak and Richardson[6] reported that the traditional concept of the senile endometrium as extremely atrophic was borne out in only 62 of 137 cases. Thirty-eight (27.7 per cent) of the 137 cases which they studied had endometrium with proliferative activity comparable to that seen in the reproductive epoch.

There have been a number of studies of the endometrium in cases of postmenopausal bleeding. The most direct study of this kind was made in 1935 by Breipohl,[7] who interpreted the endometrial changes as due to late ovarian activity.

The fact that endometrium corresponding to the proliferative variety in the menstruating female does occur after the menopause appears to fit in with the now well-established fact that estrogen may be found in the urine of females long after the menopause or after castration.

The majority of evidence points to the assumption that cystic and hyperplastic changes in the endometrium result from the excessive or unopposed action of estrin. This is most common during the latter part of the active reproductive period but may occur earlier. Novak and Martzloff,[8] in 1924, noted that cystic and hyperplastic endometrium frequently is accompanied by ovarian follicular cysts. Nelson,[9] in 1937, and others produced a comparable picture in the endometrium of experimental animals, and a cystic and hyperplastic endometrium is known to accompany the development of estrin-producing ovarian tumors.

The source of stimulus which produces activity in the postmenopausal endometrium is uncertain. Hofbauer,[10] in 1931, found that anterior pituitary extract when injected into ovariectomized guinea pigs caused congestion of the uterus and slight but definite thickening of the basal layer of the uterine mucosa. The studies of Frank, Goldberger, and Salmon,[11] in 1936, on a group of women whose ovaries by the usual criteria were physiologically inactive, pointed to an extraovarian source of estrin. Novak and Yui[12] believed that the postmenopausal endometrial hyperplasia in their cases could be attributed to the production of estrin elsewhere than in the ovary. In considering the causes of late endometrial activity, Taylor and Millen,[13] in 1938, mentioned several possibilities, namely, an ovarian hormone which comes from small functioning ovarian neoplasms, the late development of follicles or an extraovarian source.

The occurrence of follicular cysts, failure of ovulation, infrequent presence of corpus luteum, and hyperplasia of the endometrium in patients who have adenocarcinoma have been given as proof that hyperestrinism or the unopposed action of estrogen is the immediate cause of the malignancy.[14, 15] Most authors agree that hyperplasia results from unopposed estrogenic effects. Hence, since some observers believe that hyperplasia is precarcinomatous, it is easy to see why the idea has arisen that excess estrogen leads to corporal carcinoma.

Gebhard,[16] in 1892, maintained that malignant adenomas arise from hypertrophied glands in chronic endometritis.

In 1915, Schröder[17] reported a case in which adenocarcinoma had developed in a uterus which was the seat of hyperplasia. In 1923, Meyer[18] described two cases in which islands of adenocarcinoma were found embedded in the hyperplastic endometrium, much like implanted ova, and in one of these a direct transition from benign to cancerous regions was demonstrated. Horsley,[19] in 1924, reported a case which "probably developed on an hypertrophic endometritis."

Taylor,[20] in 1932, reported 85 cases of hyperplasia, 50 cases of cervical polyps, and 152 cases of adenocarcinoma of the corpus uteri. He presented evidence, which was based primarily on the cases of adenocarcinoma, that hyperplasia may be a predisposing factor in the later development of carcinoma.

Taylor reported that carcinoma later was demonstrated in two of the 85 cases in which the original diagnosis was endometrial hyperplasia. Both of these instances of apparent transformation were found to be due to failure to detect the carcinoma on first examination. He said that these two cases "illustrate the practical dangers of a confusion of hyperplasia and carcinoma due to a failure of the malignant parts of the endometrium to reach the microscope or to an erroneous interpretation of morphology. They emphasized furthermore the criticism that must be applied to cases of apparent evolution of carcinoma from hyperplasia."

Finally, Taylor remarked that "whether from a practical standpoint hyperplasia is to be regarded as precancerous and treated as such must remain an open question. The relative frequency of hyperplasia undoubtedly indicates that the individual patient with the disease is reasonably safe. Nevertheless it appears that when hyperplasia is at all marked, the possibility of a predisposition to the development of cancer should be considered and the case regarded with the same degree of suspicion now bestowed upon the diffuse forms of hyperplasia of the breast epithelium."

Novak and Yui,[12] in 1936, reported the results of a review of all cases of endometrial hyperplasia and of adenocarcinoma of the body of the uterus which they had encountered during the previous eleven years. This entailed study of 12,813 specimens, among which they encountered 804 cases of endometrial hyperplasia and 104 cases of adenocarcinoma of the body of the uterus. Of the 804 cases of endometrial hyperplasia, 40 occurred in women more

than 55 years of age, an incidence of approximately 5 per cent. Of the 104 cases of adenocarcinoma of the body of the uterus, 61 occurred in women who were more than 55 years of age, an incidence of 58.6 per cent. Moreover, of the 61 patients, 13 (21.3 per cent) had associated hyperplasia of the endometrium. Of the 104 cases of adenocarcinoma of the body of the uterus, there were 64 in which both carcinomatous and noncarcinomatous mucosa was available for study. Of these 64 cases, 25 (39 per cent) had coexisting hyperplasia of the mucosa.

Since adenocarcinoma and hyperplasia were common, Novak and Yui felt that their simultaneous occurrence was a coincidence rather than an indication of any more fundamental relationship between the two. However, these investigators found it necessary to change this concept. They concluded, on the basis of the previously mentioned study of 804 cases of endometrial hyperplasia and 104 cases of corporal adenocarcinoma, that not only do adenocarcinoma and hyperplasia frequently coexist, but often, in the same case, and perhaps even in the same section, all grades of transition from frankly benign, to borderline, to obviously malignant histologic pictures are observed. Their observations seem to indicate that hyperplasia persisting after the menopause predisposes to the development of carcinoma. Since the only known cause of hyperplasia is persisting hyperestrinism, the natural assumption is that this factor of abnormally long-continued subjection of the endometrium to stimulation with estrin is the important predisposing influence.

TeLinde[21] in discussing the paper of Novak and Yui pointed out that their findings differed from those of certain other investigators. He said, "It would seem that the most likely explanation is a difference in their interpretation of what constitutes the minimum histologic changes necessary to a diagnosis of hyperplasia." He furthermore said that there are no absolute criteria for diagnosis. TeLinde had studied the material of Novak and Yui and frankly admitted that their histologic interpretation of hyperplasia was more liberal than his. He also had studied the postmenopausal endometrium in twenty cases picked at random in his laboratory. In eleven cases (55 per cent) he found the same histologic picture which Novak and Yui had interpreted as hyperplasia. This 55 per cent incidence caused TeLinde to question the etiological significance of the 39 per cent in the carcinoma group reported by Novak and Yui. The following remarks by TeLinde are not only pertinent to the subject under discussion, but also applicable to certain other situations.

"If hyperplasia is a precancerous lesion one would expect a parallelism between the age incidence of hyperplasia and carcinoma. The greatest incidence of hyperplasia is in the fifth decade of life. After fifty the incidence of hyperplasia decreases but the incidence of adenocarcinoma increases, so instead of a parallelism in their incidence there is a divergence. I have assured innumerable women in the late forties or early fifties who have had recurring bleeding due to hyperplasia that after getting past the menopause their chance of further trouble due to the hyperplasia would be nil. I have never had one of these women return with carcinoma of the endometrium. But even if an occasional one is later a victim of carcinoma, is it more than one might expect on the law of chance?

"If we are to change our concept of hyperplasia from a purely benign lesion to a precancerous one, the next logical step is to modify our present conservative treatment in a radical direction. This I feel would be a mistake, and it is with the thought of preventing unnecessary radical surgery or radiation that I have brought up these objections to the acceptance of an attractive theory which does not coincide with my clinical or pathologic experience."

Heurlin,[22] in 1911, in a study of 44 cases of primary adenocarcinoma of the body of the uterus did not find evidence of associated hypertrophy of the endometrium but on the contrary he found an atrophic condition.

Payne,[23] in 1937, studied 2,070 sections from 534 cases (496 premenopausal and 38 postmenopausal) of endometrial hyperplasia. In the latter the time elapsing since the menopause was one to twenty-three years. In 13 of the 534 cases (2.4 per cent) there was associated carcinoma of the corpus uteri. He pointed out that if hyperplasia predisposes to carcinoma, the incidence of malignancy should exceed 2.4 per cent. Carcinoma occurred five times more often in the postmenopausal cases than in the premenopausal cases, yet

TABLE I. COMPARISON OF ENDOMETRIUM IN ADENOCARCINOMATOUS AND NONADENOCARCINOMATOUS CORPUS UTERI

DESCRIPTION AND NUMBER OF CASES	EARLY PROLIFERATIVE ENDOMETRIUM			LATE PROLIFERATIVE ENDOMETRIUM			ATROPHIC ENDOMETRIUM			EARLY PROLIFERATIVE AND ATROPHIC ENDOMETRIUM		LATE PROLIFERATIVE AND ATROPHIC ENDOMETRIUM	
	CASES	PER CENT*	TOTAL†	CASES	PER CENT*	TOTAL†	CASES	PER CENT*	TOTAL†	CASES	PER CENT*	CASES	PER CENT*
1. Classification of Nonadenocarcinomatous Portion of Endometrium in Eighty-Six Cases of Adenocarcinoma													
Adenocarcinoma, grade 1 (21 cases)	8	38.1	11	5	23.8	8	2	9.5	8	3	14.3	3	14.3
grade 2 (23 cases)	11	47.8	14	2	8.7	4	5	21.7	10	3	13.0	2	8.7
grade 3 (15 cases)	3	20.0	6	6	40.0	7	2	13.4	6	3	20.0	1	6.7
grade 4 (27 cases)	6	22.2	10	9	33.3	13	4	14.8	12	4	15.8	4	15.8
Total (86 cases)	28	32.6	41 (47.7%)	22	25.6	32 (37.2%)	13	15.1	36 (41.8%)	13	15.1	10	11.6
2. Classification of Endometrium in 150 Cases Without Adenocarcinoma													
Surgical (100 cases)	55		66	31		31	3		14	11			
Necropsy (150 cases)	14		19	26		28	3		10	5		2	
Total (150 cases)	69	46.0	85 (56.7%)	57	38.0	59 (39.3%)	6	4.0	24 (16%)	16	10.0	2	1.3

*Percentages opposite grades 1, 2, 3 and 4 represent per cent of cases for respective grade of adenocarcinoma; percentages opposite total for adenocarcinomatous and nonadenocarcinomatous uteri represent per cent of 86 and 150 cases, respectively.

†Total cases that showed respective change, regardless of whether associated with other endometrial changes. Thus, some cases are counted in two groups.

postmenopausal corporal carcinoma generally is conceded to be three to four times as common as premenopausal regardless of the type of endometrium.

Jones and Brewer,[24] in 1941, studied 68 cases of carcinoma of the corpus uteri from the standpoint of histologic and anatomic evidence of ovarian and endometrial function. They pointed out that the various reports indicate that hyperplasia is not found with any great frequency in patients who have carcinoma. Therefore, they believed it logical to assume that estrogenic stimulation adequate to cause carcinoma also would stimulate the remaining portions of the endometrium to a greater extent than that which is found. These investigators also mentioned that experimental studies on the rat, mouse, guinea pig, rabbit, and monkey had demonstrated that administration of estrogens in large quantities over prolonged periods of time had produced cystic glandular hyperplasia of the endometrium but not carcinoma, and that carcinomatous changes were induced only when some carcinogenic agent was used simultaneously.

Jones and Brewer concluded that in the presence of endometrial carcinoma, the ovaries may function normally and the uninvolved portion of the endometrium may respond normally to ovarian stimulation. Thus, the etiological significance of hyperestrinism or the unopposed action of estrin in endometrial carcinoma was not demonstrable in their cases. The corpus luteum was normal even in those instances in which all the endometrium was involved in the malignant change. Taylor[13] and Herrell[14] likewise have reported that the corpus luteum occasionally is present and apparently functioning in patients who have endometrial carcinoma.

Shaw,[25] Cullen,[3] and Burch and others[26-28] have been inclined to deny that hyperplasia is a predisposing influence in the development of carcinoma. In the most recent paper by Burch,[28] he states, "I have never seen the two conditions associated in the same patient, nor have I ever seen hyperplasia as a forerunner to cancer."

Material and Method

Material.—The material studied consisted of gross and microscopic specimens of postmenopausal uteri, detailed descriptions of specimens and clinical and operative records of 236 cases of the Mayo Clinic. The 236 cases consisted of 86 cases in which the uterus had been removed because of adenocarcinoma, 100 cases in which the uterus had been removed for other reasons, and 50 cases in which routine necropsy had been performed.

In the majority of these cases careful examination of the uterus, tubes, and ovaries was possible, although in some cases only the uterus, and in others only the uterus and one ovary were available. In order to obtain suitable specimens for the study of uninvolved endometrium in carcinomatous uteri, careful selection was necessary. Uteri in which the carcinoma had involved more than half the endometrium were not used. The cases in which necropsy had been performed likewise were carefully selected in order to include only those in which the uterus was grossly normal and not involved by any pathologic lesion which might produce an abnormal condition.

Method.—Because of the paucity of information available concerning the postmenopausal endometrium and its relation to adenocarcinoma of the corpus uteri, it was decided to study the problem from three standpoints: namely, (1) classification of uninvolved endometrium in cases of adenocarcinoma of the corpus uteri, (2) classification of endometrium in cases without adenocarcinoma of the corpus uteri, and (3) a comparison of endometrium in adenocarcinomatous and nonadenocarcinomatous uteri.

From two to six blocks were made through the wall of the uterus so that the full thickness of the endometrium, together with a sizable portion of myometrium, was included in each section. Each block was taken from a different portion of the interior of the uterus so that all the endometrium out toward the horns, as well as down to the endocervix, was included in so far as possible. At least one section was taken through the adenocarcinomatous region in those uteri in which a malignant lesion was present.

On microscopic examination the lesions were graded from 1 to 4 after the method of Broders.

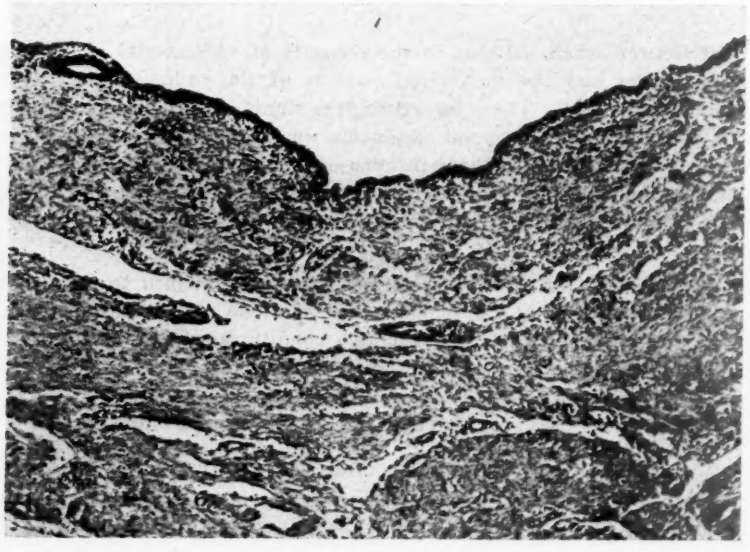

Fig. 1.—Atrophic endometrium. Section reveals single layer of surface epithelium with one gland present in the field (×70).

The endometrium was classified according to the method used by Herrell and Broders[5] in their study of the endometrium of women during the period of the normal menstrual cycle. Although the endometrium was classified as "early proliferative," "late proliferative," and so forth, and from the histologic standpoint may have been indistinguishable from that of the normally menstruating female, we are aware that the tissue may not have been proliferative in the same physiologic sense. The terms "atrophic," "early proliferative with atrophy," and "late proliferative with atrophy" also were used. The source of the estrogenic stimulus to endometrial proliferation was considered to be extraovarian.

In the specimens of endometrium classified as atrophic there was a single layer of surface epithelium with a subjacent thin layer of stroma in which there were one or two and sometimes no glands per low-power microscopic field. The stroma was not always loose and in some instances was extremely dense. Several sections of atrophic endometrium revealed no glands that resembled those of proliferative endometrium but rather glands that resembled subbasal glands, small and apparently nonfunctioning. Atrophic endometrium was found in the

uteri of those women who, as far as could be determined from the menstrual history, had passed through the menopause in a normal fashion.

The endometrium classified as either early proliferative with atrophy or late proliferative with atrophy presented the typical picture of atrophy per several low-power microscopic fields. In other fields there also was a resemblance to the typical early or late proliferative endometrium, as described by Herrell and Broders (Figs. 1, 2, and 3).

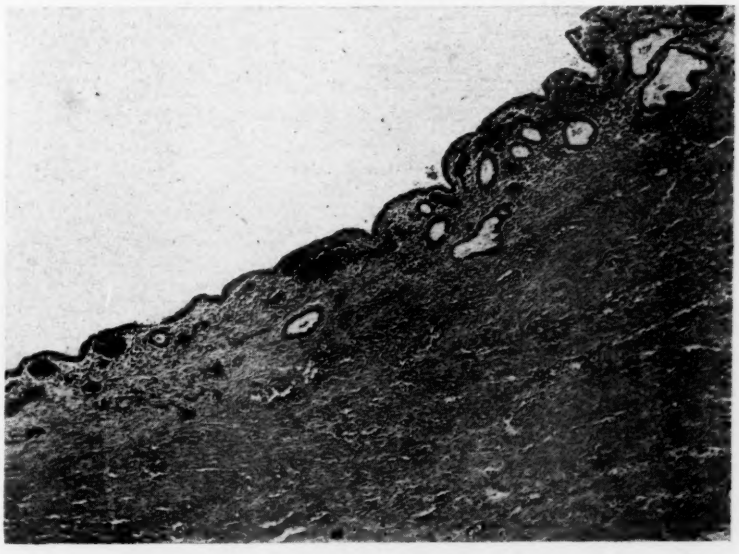

Fig. 2.—Early proliferative endometrium with atrophy. Section reveals atrophic endometrium on left of field and characteristic early proliferative endometrium on right of field (×45).

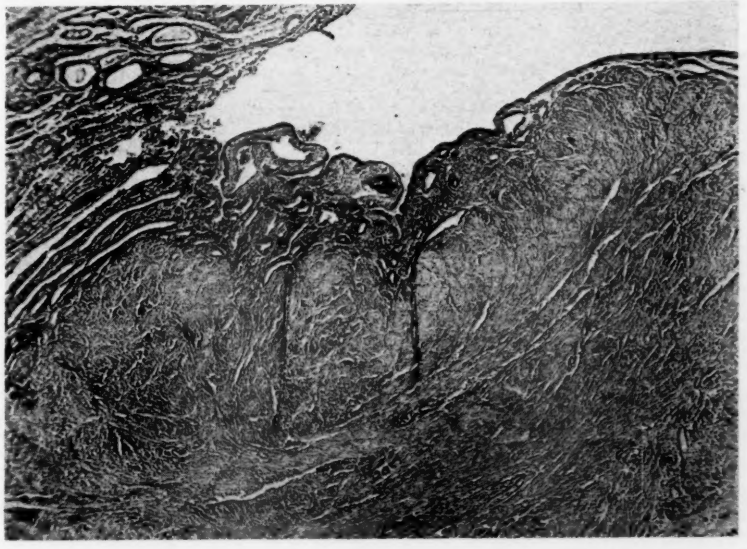

Fig. 3.—Late proliferative endometrium with atrophy. Section reveals atrophic endometrium in right portion of field together with late proliferative endometrium in left portion of field (×22).

A study was made of cystic change, accumulation of secretion, density of stroma, subbasal glands, and sclerosis of arteries and arterioles. These findings were graded on the basis of 1 to 4 per uniform field of microscopic magnification, grade 1 representing the minimal amount and grade 4 the maximal amount of

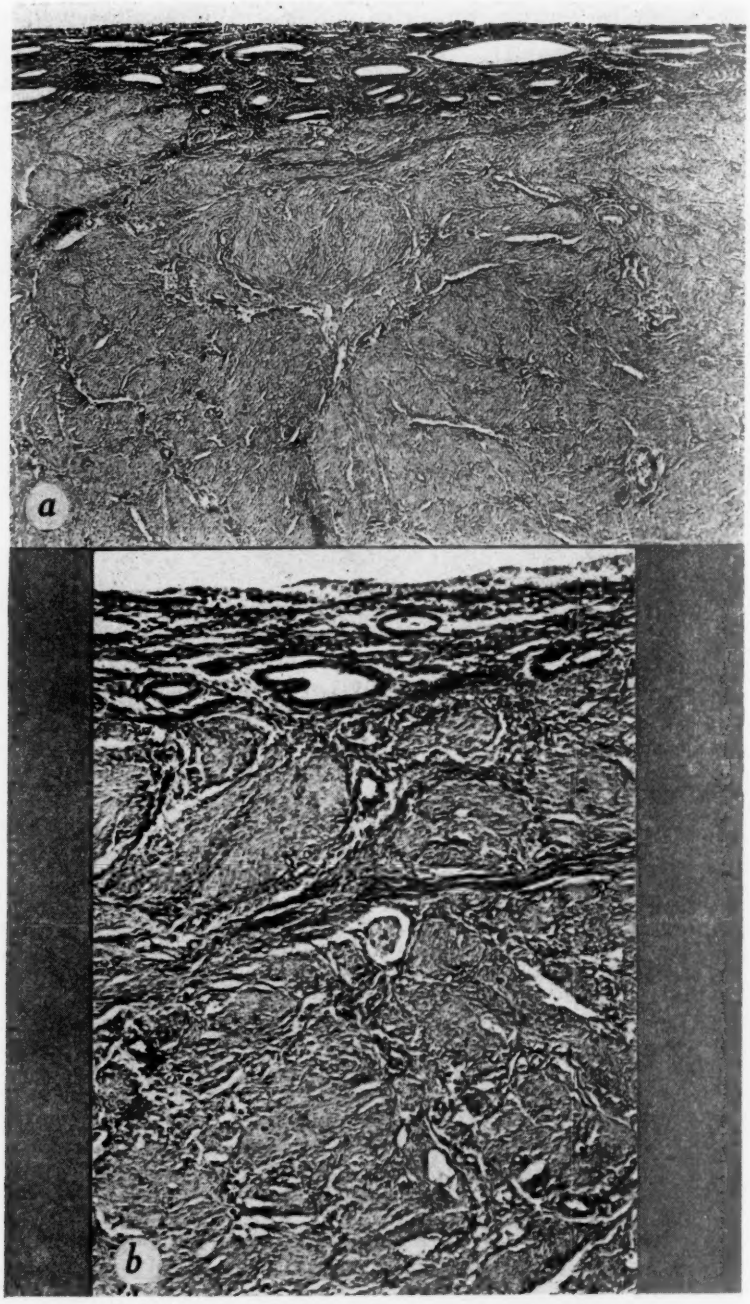

Fig. 4.—Subbasal glands, grade 1. *a*, Section reveals a few scattered subbasal glands in the lower portion of the endometrium with an occasional subbasal gland in the uppermost portion of the myometrium (×45); *b*, section reveals one subbasal gland just beneath the endometrium in the uppermost portion of the myometrium (×100, higher magnification of *a*).

such change. In classifying the cystic changes, preference for the concept that the endometrium was either early or late proliferative with cystic change was held. The gradation of 1 to 4 was made on the basis of size and number of cystic glands.

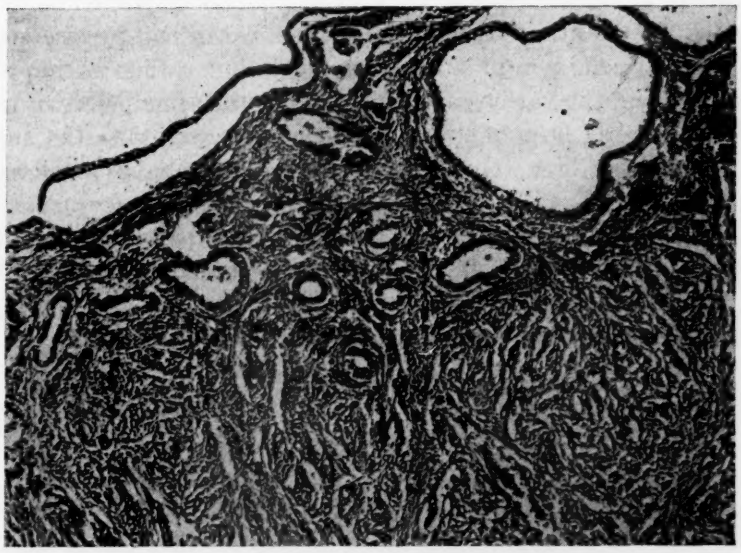

Fig. 5.—Subbasal glands, grade 2. Section reveals four subbasal glands just beneath the endometrium in the uppermost portion of the myometrium (×75).

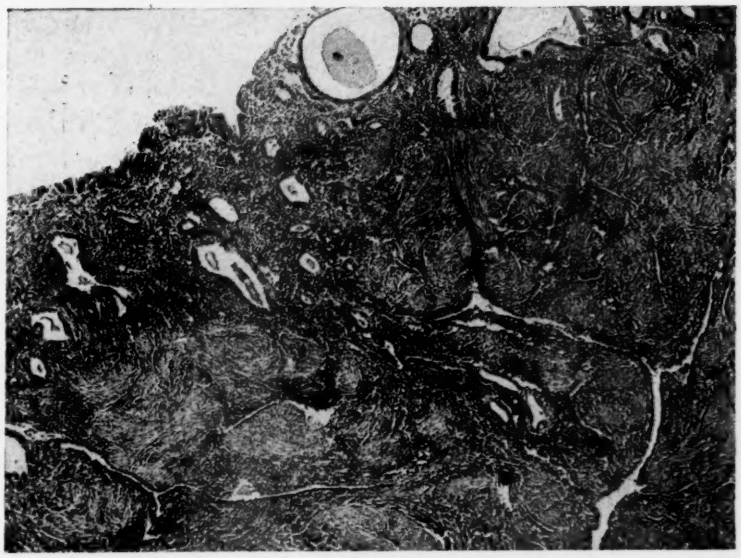

Fig. 6.—Subbasal glands, grade 3. Section reveals numerous subbasal glands deep in the myometrium but in continuity with other subbasal glands reaching up to the myometrium (×45).

The gradation of accumulation of secretion depended on the number of cystic glands containing such secretion. The nature of this secretion, which stained light purple with hematoxylin, was not investigated but it seems probable that it was mucus. Its presence in the endometrial glands gave them the

appearance of endocervical glands and apparently indicated loss of function. Although the grade of cystic change roughly paralleled the degree of accumulation of secretion, it did not invariably do so. Thus, an endometrium with grade 4 cystic change but with only grade 1 secretion might be found.

The grading of the stroma on the basis of its density was made in a qualitative rather than a quantitative sense. In other words, no precise count of the number of stromal cells per unit area was made but rather an impression was gained by comparing the various specimens under the same power of microscopic magnification. As has been reported by many investigators, the stromal cells fell into two more or less well-defined groups: namely, (1) cells resembling small lymphocytes, and (2) cells somewhat larger with pale cytoplasm and large oval-shaped, dark-staining nuclei. The decidua-like or pseudodecidual changes of the latter type of stromal cell, in which they assume an epithelioid cell appearance, were not found, probably due to the fact that no specimen which exactly resembled the differentiative type of endometrium was found.

Fig. 7.—Subbasal glands, grade 4. Section reveals a group of subbasal and endometrial glands deep in the myometrium and completely isolated from the endometrium, a condition of so-called "adenomyosis" (×40).

The subbasal glands were graded on the basis of their number per low-power field and also on their distance beneath the surface epithelium. When the tissue was graded 4, the glands were well down into, and surrounded by, the myometrium. Thus they seemed similar to glands found in cases of adenomyosis. Since it was not the purpose of this study to go into the problem of adenomyosis

in detail, the extent of involvement of the subbasal glands merely was noted and classified so that the frequency of occurrence in the adenocarcinomatous and nonadenocarcinomatous uteri could be compared. Examples of the various grades of involvement of the subbasal glands are given in Figs. 4 to 7.

In grading the sclerosis of the arteries and arterioles, those specimens in which calcium deposition was seen were graded 4.

An estimation of the general thickness of the endometrium in each case was made by averaging, with reference to three sections of tissue, the fractions of the diameter of a low-power microscopic field which was occupied by endometrium. The same degree of magnification, of course, was used throughout the study in order to obtain an accurate comparison in the adenocarcinomatous and nonadenocarcinomatous uteri.

Comment and Results

As has been observed by many investigators, postmenopausal bleeding or spotting was the chief symptom in the vast majority of cases of adenocarcinoma of the corpus uteri. This symptom occurred in 70 of the 86 cases. In 15 cases there was bloody leucorrhea. Bleeding was absent in only one case.

Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed in 74 cases, vaginal hysterectomy in 7, Wertheim's hysterectomy in 4, and subtotal abdominal hysterectomy with bilateral salpingo-oophorectomy in one. In all cases, diagnostic dilatation and curettage preceded surgical removal of the uterus.

In 21 of the 86 cases of adenocarcinoma, the lesion was graded 1; in 23 it was graded 2; in 15, graded 3; and in 27, graded 4, according to Broders' method (Table I).

The number and percentage of cases in which the various types of endometrium were found, as well as the total number of cases of early proliferative endometrium with or without associated atrophy, of late proliferative endometrium with or without associated atrophy, and of atrophic endometrium with or without proliferation, also are shown in Table I. The total number of cases that showed early proliferative, late proliferative, or atrophic changes appear in the third column under each heading; obviously, due to the fact that some cases appear in more than one column, the total number of cases and the total percentage are not 86 cases and 100 per cent, respectively. The fact should be re-emphasized that the terms "early proliferative" and "late proliferative," in order to be entirely accurate, should be qualified by the statement that such endometrium corresponds in histologic appearance to early proliferative or late proliferative endometrium, as the case may be, but that it may not be proliferative in the same physiologic sense.

The important deduction to be made from the study of 86 cases of adenocarcinoma of the corpus uteri is that the number of cases of each type of endometrium does not vary appreciably with the grade of malignancy. Of the 21 cases of grade 1 adenocarcinoma and the 23 cases of grade 2 adenocarcinoma, the greatest percentage of cases had early proliferative endometrium, whereas the greatest percentage of the grade 3 (15 cases) and the grade 4 (27 cases)

TABLE II. COMPARISON OF FINDINGS IN ADENOCARCINOMATOUS AND NONADENOCARCINOMATOUS CORPUS UTERI

	GRADE 1		GRADE 2		GRADE 3		GRADE 4		NONE	
	CASES	PER CENT*	CASES	PER CENT*	CASES	PER CENT*	CASES	PER CENT*	CASES	PER CENT*
ADENOCARCINOMATOUS UTERI (86 cases)										
Grade 1 (21 cases)										
Cystic change	2	9.5	5	23.8	5	23.8			9	42.9
Accumulation of secretion	2	9.5	7	33.3	3	14.3			9	42.9
Density of stroma	2	9.5	10	47.6	9	42.9				
Subbasal glands	5	23.8	2	9.5	3	14.3	3	14.3	8	38.0
Sclerosis of arteries and arterioles	8	38.0	5	23.8	7	33.3	1	4.8		
Grade 2 (23 cases)										
Cystic change	7	30.4	2	8.7	3	13.0	1	4.4	10	43.4
Accumulation of secretion	6	26.0	5	21.7	1	4.4			11	47.8
Density of stroma	2	8.7	9	39.0	9	39.0	3	13.0		
Subbasal glands	6	26.0	3	13.0-	4	17.4			10	43.4
Sclerosis of arteries and arterioles	5	21.7	10	43.4	4	17.4	3	13.0	1	4.4
Grade 3 (15 cases)										
Cystic change	3	20.0	5	33.3	2	13.4			5	33.3
Accumulation of secretion	4	26.8	4	26.8	1	6.7			6	40.0
Density of stroma	2	13.4	9	60.0	4	26.8				
Subbasal glands	7	46.7	1	6.7	3	20.0	2	13.4	2	13.4
Sclerosis of arteries and arterioles	3	20.0	4	26.8	7	46.7	1	6.7		
Grade 4 (27 cases)										
Cystic change	7	25.9	3	11.1	3	11.1	2	7.4	12	44.4
Accumulation of secretion	5	18.5	6	22.2	2	7.4	2	7.4	12	44.4
Density of stroma	6	22.2	11	40.7	10	37.0				
Subbasal glands	7	25.9	8	29.6	1	3.7	3	11.1	8	29.6
Sclerosis of arteries and arterioles	2	7.4	11	40.7	13	48.1			1	3.7
ADENOCARCINOMA, ALL GRADES (86 cases)										
Cystic change	19	22.1	15	17.4	13	15.1	3	3.5	36	41.8
Accumulation of secretion	17	19.8	22	25.6	7	8.1	2	2.3	38	44.1
Density of stroma	12	14.0	39	45.3	32	37.2	3	3.5		
Subbasal glands	25	29.1	14	16.3	11	12.8	8	9.2	28	32.6
Sclerosis of arteries and arterioles	18	20.9	30	34.8	31	36.0	5	5.8	2	2.3
NONADENOCARCINOMATOUS UTERI (150 cases) (100 surgical; 50 necropsy)										
Cystic change										
Surgical	43		20		10		1		26	
Necropsy	11		19		12		4		4	
Total	54	36.0	39	26.0	22	14.7	5	3.3	30	20.0
Accumulation of secretion										
Surgical	31		5		1		1		62	
Necropsy	19		7		4		1		19	
Total	50	33.3	12	8.0	5	3.3	2	1.3	81	54.0
Density of stroma										
Surgical	21		34		24		21			
Necropsy	9		18		14		9			
Total	30	20.0	52	34.6	38	25.3	30	20.0		
Subbasal glands										
Surgical	14		22		14		16		34	
Necropsy	5		5		11		2		27	
Total	19	12.7	27	18.0	25	16.7	18	12.0	61	40.6
Sclerosis of arteries and arterioles										
Surgical	38		46		14				2	
Necropsy	24		7		4		5		10	
Total	62	41.3	53	35.3	18	12.0	5	3.3	12	8.0

*In group of adenocarcinomatous uteri, grades 1, 2, 3 and 4, the percentage figures represent per cent of cases for respective grade of adenocarcinoma; in group of adenocarcinomatous uteri, all grades, the percentage figures represent per cent of 86 cases; in group of nonadenocarcinomatous uteri, the percentage figures represent per cent of 150 cases.

had late proliferative endometrium. However, when the cases of early proliferative endometrium are added to the cases of late proliferative endometrium to obtain the total cases of proliferative endometrium, whether late or early, no appreciable variation in percentage with the grade of malignancy is evident. The percentage of cases of proliferative endometrium, grade 1, was 61.9; grade 2, 56.5; grade 3, 60.0, and grade 4, 55.5. Likewise, there was no noteworthy variation in the percentage of cases of atrophic endometrium, irrespective of the grade of adenocarcinoma. The percentage of cases of atrophic endometrium, grade 1, was 9.5; grade 2, 21.7; grade 3, 13.4; and grade 4, 14.8.

No instance of endometrium corresponding exactly to differentiative endometrium was found. There were two cases that had some features similar to differentiative endometrium but these were finally classified as corresponding to the late proliferative variety.

A similar histologic examination was made of the 150 uteri that were not involved by adenocarcinoma (Table I), and a comparison of the totals in the two groups of cases shows no appreciable difference in the percentage of cases of each type of endometrium. In fact, the percentages run consistently similar in the two groups of cases. One noteworthy discrepancy exists in the cases of atrophic endometrium, the percentage of this condition in adenocarcinomatous uteri being 41.8 as compared with 16 in nonadenocarcinomatous uteri. This is suggestive, although indirect, evidence against the concept that hypertrophy predisposes to the development of carcinoma. In fact, it seems to indicate that corporal carcinoma tends to occur more frequently in uteri in which there are atrophic changes in the endometrium than in those in which there are not.

The cystic changes, accumulation of secretion, density of stroma, subbasal glands and sclerosis of arteries and arterioles for both the adenocarcinomatous and nonadenocarcinomatous cases are graded in Table II. The percentage of cases with cystic change and accumulation of secretion graded 3 and 4 is roughly the same in the two groups. Thus, this study does not substantiate the theory that this type of endometrium predisposes to uterine malignancy. It also may be significant that in the adenocarcinomatous group, 41.8 per cent of cases showed no cystic changes, whereas only 20 per cent of the nonadenocarcinomatous group had no cystic changes. The percentages of stromal density, grade 1 and grade 2, and of grade 3 and grade 4 are roughly the same in the two groups. The fact that there was no consistent difference in the presence of subbasal glands would tend to indicate that they have no causal relationship to uterine carcinoma. The same may be said in so far as the degree of sclerosis of arteries and arterioles in the subendometrial tissues and muscularis is concerned.

There was virtually no difference in the average thickness of the endometrium in the two groups. The average thickness measured in fractions of the diameter of a low-power microscopic field was as follows: adenocarcinomatous uteri, 0.3 to 0.36; nonadenocarcinomatous uteri, 0.3 to 0.4; surgical cases 0.36, necropsy cases 0.3.

A detailed study of adenomatous polypi was not made because in all cases, as previously mentioned, dilatation and curettage had been performed. Thus, some of the existing polypi undoubtedly had been removed. Four uteri in which

TABLE III. DATA CONCERNING 236 WOMEN IN THE POSTMENOPAUSAL STATE

	ADENO-CARCINOMATOUS UTERI	NONADENOCARCINOMATOUS UTERI	
		OPERATION FOR CONDITION OTHER THAN CARCINOMA	ROUTINE NECROPSY
Cases	86	100	50
Age, years	39 to 80	49 to 78	50 to 93
Average age, years	53	61	63
Time since menopause	2 mo. to 25 yr.	1 mo. to 30 yr.	1 mo. to 43 yr.
Average time since menopause	7 yr.	12 yr.	14 yr.
Para 0, gravida 0	23	29	18
Average gravidity and parity	3-3	3-3	3-3
Associated pathologic condition			
No cysts in ovaries	33	36	20
Fibromyoma			
Single	11	14	3
Multiple	19	23	9
Adenomatous polyp			
Single	1	8	7
Multiple	3	14	3
Adenomyoma	2	5	2 (1 in round ligament)
Endométrioma	1	2 (ovary)	1 (ovary)
Carcinoma showing regions of squamous-cell metaplasia	3		
Carcinoma simulating			
Sarcoma	1		
Squamous-cell epithelioma	1		
Cervix, carcinoma grade 2 to 4	1		
Chronic cervicitis	31	66	40
Cystic cervicitis	18	28	6
Cystic adenomatous polyp of cervix	3	6	4
Cysts of Morgagni			
Single	1	2	1
Multiple		3	1
Intracystic carcinoma (ovary)		2	1 (small)
Metastatic carcinoma (ovaries)		1	1 (small)
Fibroma (ovaries)	3	2	3
Intracystic fibroma (ovary)			1
Multilocular cyst (ovary)		1	1
Cystic oophoritis (bilateral)	7	11	6
Chronic oophoritis with papillary cystadenoma (left ovary)	1		
Chronic oophoritis			
Right	2		
Bilateral	7	12	5
Dermoid cyst (left ovary) and atrophy (right ovary)	1		
Bilateral atrophic ovaries	49	82	42
Adenocarcinoma, grade 4 (one ovary), and bilateral ovarian cystadenomata	1		
Metastatic nodule on right ovary with chronic oophoritis on left ovary	1		
Luteinization (ovaries)	4	9	5 (no cysts)
Corpus luteum			1 (aged 63 yr.; 25 yr. past menopause)
Hydrosalpinx			
Single (with other chronic salpingitis)	1	4	3
Bilateral	2	6	3
Metastatic adenocarcinoma (right tube) and chronic salpingitis (left tube)	1		
Bilateral chronic salpingitis	58	72	38
Atrophic tubes	11	14	6
Multiple carcinomas in uterus	1		

polypi were present were found in the 86 cases of adenocarcinoma, an incidence of 4.7 per cent (Table III). Twenty-two polypi were found in the 100 cases in which the uteri had been removed for other conditions, an incidence of 22 per cent. Ten were found in the 50 cases in which necropsy had been performed and in which no malignant lesion was present, an incidence of 20 per cent. These figures suggest that polypi occur with considerably less frequency in uteri in which adenocarcinoma is present than in those without adenocarcinoma. This seems to be incompatible with the generally held conception that uterine polypi are precarcinomatous; however, the figures are merely suggestive.

Additional information concerning the 236 cases studied, including the associated pathologic conditions found on gross examination of the specimens, is shown in Table III. These findings are included merely for completeness.

Summary and Conclusions

The material studied consisted of postmenopausal uteri in 236 cases. In 86 of these cases the uterus had been removed because of adenocarcinoma, and in 100 cases it had been removed for other reasons. In 50 cases routine necropsy had been performed.

In the group of 86 women who had adenocarcinoma of the corpus uteri, all but one had had vaginal bleeding or spotting as a presenting complaint.

In the 86 cases of adenocarcinomatous uteri there was no appreciable variation in the percentage of cases with proliferative endometrium, whether early or late, or in the percentage of cases with atrophic endometrium, according to the grade of malignancy.

There was no appreciable difference in the percentage of cases of any given type of endometrium in adenocarcinomatous uteri as compared with nonadenocarcinomatous uteri, except with regard to atrophic endometrium. Thus, 41.8 per cent of cases of uteri with malignancy showed atrophic endometrium and only 16 per cent of cases of uteri without malignancy showed atrophic endometrium. This suggests that adenocarcinoma of the uterine corpus is more likely to occur in cases in which there is atrophy of the endometrium than in cases in which there is no atrophy.

Two of the 86 cases of adenocarcinomatous uteri and three of the 150 cases of nonadenocarcinomatous uteri presented some features similar to those found in early differentiative endometrium but since they were not entirely the same the endometrium was classified as late proliferative.

The percentage of cases with grade 3 and 4 cystic change and with grade 3 and 4 accumulation of secretion was roughly the same in the two groups of cases. Approximately 42 per cent of adenocarcinomatous uteri showed no cystic changes, whereas 20 per cent of nonadenocarcinomatous uteri showed no cystic changes. This lends evidence contrary to the view that the "Swiss-cheese endometrium" of Novak has any features predisposing to the development of carcinoma.

There was no consistent difference or variation of cystic change, accumulation of secretion in the glands, density of the stroma in and beneath the endometrial epithelium, involvement of the subbasal glands or sclerosis of the arteries

and arterioles, according to the grade of adenocarcinoma. In 28 of the 86 cases no subbasal glands were found. Thus, subbasal glands seem to have no causal relationship to adenocarcinoma of the uterus.

There was virtually no difference in average thickness of endometrium in adenocarcinomatous uteri as compared with nonadenocarcinomatous uteri.

The incidence of endometrial polypi in uteri without adenocarcinoma was roughly eight times greater than their incidence in uteri containing adenocarcinoma. However, previous curettage in all cases of malignancy might be partially responsible for the variation.

In general, it may be concluded from this comparison of adenocarcinomatous and nonadenocarcinomatous uteri removed from women who had passed the menopause, that the uninvolved portion of endometrium in the former group was in no demonstrable way different from that of the endometrium in the latter group except that atrophic endometrium was found more often in adenocarcinomatous uteri than in nonadenocarcinomatous uteri, while endometrial polypi were found more often in nonadenocarcinomatous uteri.

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THE ANOVULATORY CYCLE AND MENSTRUATION

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THE concept of an "anovulatory cycle" is the product of anatomic and biologic investigations, which are not only of interest, but of practical importance, to the gynecologist. The classical studies of Corner[5, 6] and Hartman[12] were the first in the field and are too well known to require detailed restatement. Anovulatory bleeding has been termed menstruation due to some similarity of the former to the latter, but I want to show that they differ in essential details. Among the similarities is the recurrent nature of both, particularly in the monkey. In this regard there could be no objection to the term anovulatory cycle, since proliferative changes in the ovary and the endometrium pass into regression, and return to their original state. This is not necessarily rhythmical since the term rhythmical denotes a regularity in the time of recurrence at least approximating that of menstruation in the normal healthy woman.

What Is the Anovulatory Cycle?

Similarities and Differences With Menstruation.—Anovulatory bleeding represents a premature interruption of the menstrual cycle. Does the interruption of the cycle occur only at the time when the rupture of the follicle should take place, or can the interruption occur at any time before or after the rupture? This question is important since, at the time of anovulatory bleeding, the endometrium of monkeys shows various degrees of proliferation, as is evident in the pictures appearing in the works of Corner and others.

A brief summary of the known changes which occur in anovulatory bleeding is as follows: The follicle regresses while the endometrium is still in the proliferation phase. Anovulation occurs with the shedding of a thin necrotic superficial layer of the endometrium. These two features, the involution of the ripened follicle and of the proliferating endometrium, clearly belong to the basic picture of the anovulatory cycle. The condition of the egg cell is unknown.

Not only is the incidence of anovulatory bleeding in the human unknown, but too little is known of the extent of the follicular development, and the details of its regression in anovulatory bleeding. This is particularly true if one requires histologic control of the ovaries for diagnosis. Some authors have described anovulatory bleeding on endometrial findings in young girls and sterile women. Others using large quantities of material for investigation (R. Schroeder,[21] R. Meyer),[20] have also reported the frequent discovery of functionless endometrium in young girls and women who reported regular bleeding. In the majority of these cases, however, the endometrium was

either poorly developed or even atrophic. Only occasionally was there sufficient response to justify a diagnosis of normal proliferation phase.

Under any circumstances, it would appear that the similarity of function between the monkey during periods of anovulatory bleeding, and the girl at puberty, has been overemphasized. Gambarow[10] concluded from his studies that it is doubtful if it occurs at all. The ability of young girls to conceive has been studied in large numbers in Russia, and he was able to report on 22 cases in which conception occurred in girls of thirteen to fifteen years of age and before menstruation began. It is remarkable that pregnancies may occur in one to three months after the beginning of intercourse and before the onset of menstruation. These findings confirm those reported from India where marriage at twelve years of age is not uncommon.

Immediately following the surprising discovery of the process of anovulatory bleeding, much emphasis was placed on its rhythmic recurrence; but, as a matter of fact, this is very rarely the case. Allen[1] describes as a peculiarity the regular recurrence of such bleeding eight times in a monkey, but endometrial hyperplasia may show an equal regularity of bleeding episodes, and there is no doubt that this is a pathologic condition. It has the same hormonal background as anovulatory bleeding except that in the case of hyperplasia, the effect is continued over a longer period of time. Since some similarities exist between anovulatory and ovulatory bleedings, the bleeding and necrosis with shedding of the endometrium, added to the rough regularity of recurrence, soon gave rise to the term "anovulatory menstruation." During the summer time the anovulatory cycle in monkeys in captivity is a common occurrence. Joachimovits[13] states, on the basis of his studies, that anovulatory bleeding is exceptional in monkeys in the tropics. So it seems to be clear that captivity acts like domestication on the regularity of the anovulatory cycle.

Interruption in early premenstrual endometrium is described by Corner[6] (1939) in a monkey after an operation. But this also happens in women, as Bartelmez[3,a] has pointed out. I can illustrate such a case in a 25-year-old woman. The menses were formerly regular. For one year following an abortion, the menses were irregular. A curettage was done on the second day of bleeding, which started eighteen days after the beginning of the last period. As shown in Fig. 1, the surface everywhere had been cast off; the remaining endometrium was in decay. The glands were moderately tortuous, and the epithelium contained glycogen in the upper parts of the cells.

I believe that this case constitutes a premature interruption of the cycle in the early secretory phase.

Such bleedings may also occur in humans during the menarche, lactation, and climacterium, as some observers maintain, but mostly the histologic picture is so irregular that it does not resemble the normal proliferative phase. If these bleedings appeared during the active sexual life of women, they would be abnormal disturbances.

The definition of anovulatory bleeding as recurrent bleeding from the shedding of a proliferated endometrium suggests that it occurs just before the time when ovulation might be expected, and so is associated with manifestations

of estrus. This at once suggests the similarity to the regression which occurs at the end of estrus in the lower animals when copulation has not taken place. Even in those animals where estrus is associated with bleeding, no reasonable basis exists for identifying it with menstruation. They are, rather, two different kinds of regression as is acknowledged generally now. In the primate, the cycle normally continues after estrus as a special pregravid phase, while in lower animals it reaches an abrupt end after estrus, and is thus comparable to anovulatory bleeding.

If estrus bleeding and menstruation in different animals are not the same, then anovulatory bleeding and menstruation when both happen in primates, are not comparable either. In both estrus bleeding and anovulatory bleeding, the pregravid phase of the primate is missing.

Fig. 1.

Phylogenesis and Menstrual Cycle

Allen, Hisaw, and Gardner,[2] in comparing the estrus cycle in the lower animals with the menstrual cycle in the primates, state: "Why this degenerative phase is accompanied by menstruation in many primates is still unknown." How the evolution of these functions have come about is a fundamental problem in phylogenesis and biogenesis.

Certain features of the problem may, however, be worth discussing. At first glance it might be thought that this had little to do with the problem at hand, but I believe that short consideration of the general background of menstruation may establish a broader concept, which will be useful in discussing the relation between menstruation and anovulatory bleeding.

First of all, it may be stated that menstruation must not be considered apart from its relation to the cycle and to the whole sex function. Only a few decades ago, the interest of the gynecologist was focused upon the process of menstruation as though it were the most important event in the natural history of women. At that time a distinction had been drawn between a true and a false corpus luteum. It is now a matter of general knowledge that there is but one corpus luteum, and that it is either living and functioning

in the pregravid phase and in pregnancy, or dying and functionless during menstruation and post partum. In this regard, it was even difficult to get general acceptance of the fact that the masses of stainable lipids in the luteal cells during and after menstruation did not represent function but were actually nothing but decomposition products. At the present time there is general agreement that the cycle changes, in both the ovary and endometrium are in every respect a preparation for the anticipated pregnancy. It appears to be still necessary, however, to point out that menstruation should not be considered apart from the other phases of the pregravid changes of the cycle.

The designation of menstruation as an "abortion" now may serve its purpose in making more plausible the explanation of the difference in mechanism between menstruation and the simpler forms of involution in the lower animals. In a general way, though not in all details, an explanation may be had by referring to differences in the relation between placental and maternal tissue.

The placentas of different species vary widely. Various terms have been applied to describe these placentae verae and semiplacentae or apposed and conjoined placentas. Grosser[11] has suggested a more detailed classification. These are, in order of increasing degrees of contact and invasion, placentae epitheliochorialis, syndesmochorialis, endotheliochorialis and hemochorialis. These describe the degree of connection between the placental chorion and the more superficial or deeper parts of the uterine tissue, namely, the epithelium, connective tissue, endothelium of the vessels, and maternal blood. It is easy to understand that the endometrium in the preparation for pregnancy must progress to a stage adequate for the varying degrees of aggressiveness of the chorion specific to every species. This involves special histologic and chemical preparations of the maternal tissue needed for the specific type of nutritional requirement of the ovum. Indeed, even before fertilization, the endometrium reacts by pregravid changes, specific for each species. The differences in these changes are particularly evident when one compares the primate with some lower animals.

In the primate, the decidua and its vessels are developed in a remarkable degree, in order to satisfy the angiotactic demands of the fetal chorion which, in this case, will form a hemochorial placenta.

The changes of the human endometrium pass in the second half of the cycle to those which satisfy the requirements of implantation and pregnancy. The connective tissue begins to show decidual change first in the neighborhood of the vessels and later more diffusely. The endothelium of the capillaries in the superficial layer of the endometrium are delicate and fragile. The musculature is quite loose and softened. These changes advance during early pregnancy.

In his excellent description of a normal human ovum in a very early stage, Brewer[4] pointed out that in the endometrium the vascular phenomena of vasoconstriction and dilatation, superficial ischemic necrosis, superficial venous congestion, extravasation, and reduced arterial flow are similar to those described

for menstruation. These vascular phenomena serve to prepare and maintain a site suitable for implantation and growth of the young ovum. The most interesting of these phenomena, carefully described by Brewer,[4] is the ischemic necrosis in the superficial layer of the endometrium. This is independent of the direct influence of the trophoblast, and is similar in every detail to the ischemic necrosis seen in the endometrium during menstruation. In this connection it might be pointed out that, not only all other pregravid changes of the endometrium of the primate, but also the vascular reactions immediately preceding menstruation, are the same as in early stages of pregnancy.

There is evidence that the histologic changes in the endometrium in preparation for pregnancy correspond to the specific requirements of the ovum of the given species. Further, in some species the endometrium undergoes changes to accommodate itself to the gross form of the ovum. These changes precede nidation. All of this has been but briefly mentioned, but it would seem to explain satisfactorily the various types of involution of the endometrium in lower animals and primates, if fertilization does not occur. It also points again to the fact that menstruation should not be forced out of its natural associations, but should be described as the breaking down of a primate endometrium which has undergone changes, and reached a stage corresponding histologically and hormonally to that of an early pregnancy.

Recently some authors have greatly emphasized the constriction of the coiled arteries and resultant ischemia which occurs in the endometrium in connection with both anovulatory and menstrual bleeding. Markee[14-19] was able to transplant endometrium into the anterior chamber of the eye and to observe the ischemia which preceded both menstrual and anovulatory shedding. This demonstration was said to remove the last doubt that anovulatory bleeding could be anything but a normal process. It must be pointed out, however, that the appearance of ischemia is a preliminary disturbance in almost all forms of necrosis, both pathologic and experimental.

Daron[7] was able to show a significant difference in the coiled arteries of the endometrium of the ovulatory and anovulatory cycle. In the *Macaca rhesus* monkey, the coiled arteries continue to differentiate during the pregravid phase while the endometrium increases only slightly in thickness during this time. In the first half of the cycle, the endometrium increases rapidly in thickness while the arteries differentiate slowly. With menstruation, the arteries at the surface are completely occluded. The deficient arterial development in the anovulatory cycle indicates that menstruation is not imminent. In anovulatory bleeding, the coiled arteries are not at the surface and their terminal arterioles are still intact even though some tissue may have been lost.

This is not the place to abstract Daron's important work at length. Only one finding will be mentioned. He was able to demonstrate that the arteries on the nineteenth and twenty-first days of the anovulatory cycle did not show the degree of development achieved by the sixteenth day of the ovulatory cycle. This can be considered as retardation of the development in the anovulatory cycle, which will not allow it to appear as a normal process.

There is another difference between the two processes, which is brought about by differences in hormonal effects. Anovulatory bleeding is caused by a destruction of a nonsecretory endometrium. In true menstruation only that part of the endometrium which has undergone secretion phase changes becomes necrotic, while the nonfunctioning basalis is retained. The most important morphologic differences between ovulatory menstruation and anovulatory bleeding have been pointed out. A comparison shows that they have little in common.

It is also evident that the morphologic differences correspond well to the functional differences. The pregravid changes of the endometrium may be considered as the most important feature of the cycle. The excretion from the endometrium of arsenic, iodine, phosphorus, calcium, magnesium, and sulfur gives to menstruation a secondary, but important, significance as a channel for the removal of toxic substances (L. Fränkel,[9] O. Grosser,[11] R. Schroeder[21]). This is not reproduced in anovulatory bleeding.

Experimental Research

Now are there any experimental results regarding the mechanism of hormonal regulation in anovulatory bleeding, which might justify placing it on a par with menstruation? From his hormonal experiments, Corner draws the following conclusions: "In the normal cycle the uterus will not bleed during the first half (follicular phase), because the ovaries are furnishing estrin. It will not bleed during the second half of the cycle (corpus luteum phase), because the corpus luteum is furnishing progesterone. The production of estrin in all probability continues. By an assumption, however, the corpus luteum undergoes retrogression, the animal is suddenly deprived of the action of both estrin and progesterone, and the endometrium breaks down. Ovulatory menstruation is thus a special case of estrin-deprivation bleeding."

This ingenious hypothesis does not find agreement with other experimental work. Engle,[8] in quoting the hypothesis of Corner, makes some remarks which are based on the findings of Markee. If, during the pregravid phase, progesterone merely prevents the protective function of the estrogen as Corner suggests, it also circumscribes the action to a period of twenty-four hours.

Engle pointed out that in both the normal ovulatory bleeding and anovulatory bleeding, the application of progesterone inhibits bleeding but estrogen does not. If any conclusion is to be drawn from this experiment, we should have to ask if the lack of progesterone enables the estrin to cause necrosis and bleeding. Reynolds states that continued injections of estrin as a maintenance dosage gives rise to occasional uterine bleeding. He concludes: "This betokens an inherent alteration in the sensitivity of the uterus to hormone under continued uniform stimulation." We might ask if this is the same way in which bleedings occur in hyperplasia, or are they caused by intermittent lack of estrin? It appears more reasonable that the withdrawal of either hormone permits conditions to develop within the vascular supply or the tissues of the endometrium

which lead to the phenomena of menstrual bleeding. Only the time of onset is different.

Smith and Engle[22] showed that after the withdrawal of estrogen, bleeding did not appear if the estrogen were replaced by progesterone. After the withdrawal of progesterone, bleeding occurred and was not prevented by estrogen in large doses. This seems to verify the conception that menstruation is caused by the cessation of progesterone action on the endometrium.

According to Engle, the character and duration of the bleeding resulting from withdrawal of either hormone are the same, but the time interval for each is different: for estrogen, 9.2 days, with a range of 6 to 16 days; and after progesterone treatment cessation, 2.9 days, with a range of 2 to 4 days.

The longer duration of regression in the follicle is certainly at variance with the usual sudden regression of the corpus luteum. If one can apply the results obtained from experimental withdrawal of estrin to anovulatory bleeding, the conclusion would be reached that regression of the follicle has preceded the bleeding by an average of 9.2 days with a range of 5 to 6 days. This range is so great that we would expect to be able to find the different stages of follicle regression. Or is the experiment not comparable with the natural process?

The knowledge of hormone relationships, while incomplete, has advanced to the stage which justifies Corner's[6] conclusion that the only possible explanation of natural menstruation is on the basis of the recurrent function and loss of function of the corpus luteum. This is in complete agreement with the observations and conclusions of R. Schroeder, R. Meyer, and others. There is no difference between Corner's opinion and ours as he seems to believe.

Conclusions

From the preceding, then, it seems clear that the results of both the histologic and hormonal investigation of anovulatory bleeding are still grossly incomplete. The findings do not yet agree well with the hypotheses. An objective consideration of the details of what is known of ovulatory and anovulatory bleeding leads to the conclusion that, although some similarities exist, the differences between the two are such as to exclude the propriety of considering them to be identical. It is scarcely necessary to present further evidence in support of the statement that a sharp line can be drawn between anovulatory bleeding and menstruation. The line separating them is clear, clearer even than between benignity and malignancy, or between physiologic and pathologic inflammation.

The limited definition of menstruation is essential for a proper perspective. In the absence of this, many technical difficulties arise. If one recognizes two types of menstruation, one must also describe two different premenstrual conditions.

Whether similarities justify the classification of ovulatory and anovulatory cycles under a common heading is another question. Both might be considered as abortive processes. The anovulatory cycle may be compared to the prepubertal interruption of the developing follicle without bleeding, while on the

other hand the cycle which ends with menstruation is more comparable to the abortion of an early pregnancy. These four types of abortive processes are determined by the death of the ovum. The difference between the abortion of the early pregnancy and the other three does not require further discussion, but one may point out the close histologic and hormonal relationships between the pregravid stage and the early pregnancy. This is the cardinal point from the gynecologist's point of view, as he will not fail to recognize the significance of the anovulatory cycle. It is important to keep clearly in mind the fact that the regular recurrence of bleeding does not necessarily signify menstruation. This is occasionally determined by the examination of curettage material. There is now every reason to believe that in the absence of another evident cause of sterility, the endometrium of these patients should be thoroughly examined before the anticipated bleeding.

For the gynecologist, the essential feature of the whole problem revolves about fertility. This is not only important to the woman concerned, as an individual physiologic process, but is a point of great biologic significance in the broad biology of perpetuated life.

It is in this broad field that the gynecologist acts as custodian. He must count on the relation of a true menstrual cycle and potential fertility. Only under these circumstances is there hope that the function of reproduction will be completed. This should be the thought of every gynecologist and should explain his objection to the use of the term menstruation for other processes. The term menstruation is not a meaningless word or a matter of opinion. It represents a function that carries the significance of a long historic background and has a scientifically determined, sharply circumscribed meaning, the goal of which is life.

The whole question, then, is not a simple academic argument, but represents the clashing of two thought processes. The biologist thinks in terms of etiology and the gynecologist in terms of ultimate ends.

Summary

The uterine bleeding, called anovulatory cycle, does not appear at a definite point in the cyclical changes of the follicle and the endometrium. Interruption of the cycle in either causes bleeding both in the early and in the late time of proliferative stage, and occasionally at any time in the luteal stage.

The similarities between true menstruation and the anovulatory cycle, namely, the ischemic necrosis and bleeding caused by the nonproduction of hormones, are superficial when compared with the fundamental differences. These latter are stipulated by the revolutionary hormonal, chemicofunctional, and morphologic preparations of the endometrium for pregnancy. These preparations in the primate differ from those in the lower mammals, because they must be adapted to very different types of placentation. For this reason the regression of the endometrium when fertilization does not occur must necessarily also be fundamentally different, so that one cannot relate estrous bleeding to menstruation.

The fact that experimental biology and gynecology consider the problem from entirely different angles gives rise to their opposing positions. Because the gynecologist thinks in terms of ultimate ends, he will not allow the term menstruation to stand for anything except that which has been traditional. It is the symbol of sexual maturity and potential fertility. Without corpus luteum there can be no pregravid phase, without which there is no true menstruation.

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SELECTIVE TREATMENT OF ANTEPARTUM HEMORRHAGE*

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IF WE were to adopt any standard method for the treatment of all cases of antepartum hemorrhage, cesarean section would be the method of choice. To justify any other procedure the results must approach those of cesarean section. Where section is the routine treatment for these patients, it is probable that future pregnancies, particularly in the case of primiparas, will also be delivered by section. To the risk of the first operation, therefore, must be added the risk that the patient will undergo in future pregnancies. For many years on our service, hemorrhage in the last trimester of pregnancy has been treated in a selective manner. After consideration of all the circumstances of the case, the method of treatment for any particular patient is determined on the basis of obstetric judgment, and I present here the results of this policy over a period of seventeen years.

Hemorrhage remains one of the three great destroyers of women in childbirth, and is far less amenable to prophylactic measures than either puerperal sepsis or the toxemias of pregnancy. Postpartum hemorrhage can be minimized by proper prophylactic measures, but in antepartum hemorrhage, prophylaxis plays very little part, except in cases of toxemia with separation of the placenta. I wish to eliminate from discussion all bleeding previous to the last trimester and, for practical purposes, this leaves us with only placenta previa and accidental hemorrhage. Occasionally a patient is seen in labor who is having more bleeding than can be accounted for by normal show. We suspect that we are dealing with partial separation of a normally situated placenta or with placenta previa, yet the case may terminate spontaneously and successfully, and careful examination of the placenta fails to reveal which, if either, of these conditions was present. Some of these patients may have excessive show from the dilating cervix or due to separation of the membranes in the lower uterine segment. In others it may be due to a low-lying placenta or to a slight separation of a placenta that is normally situated. In this study an attempt has been made to eliminate all such cases. Diagnosis may be uncertain when the patient is first seen, but becomes clear as labor progresses, or after its termination.

The diagnosis between placenta previa and accidental hemorrhage is usually easily made. However, there are frequently cases where the differentiation between the two conditions will not be obvious when the patient is first seen. The bleeding may be slight, the patient in labor, and no evidence of toxemia may exist, yet the placenta may not be palpable at the lower uterine segment. It is obvious that there must be a site for placental attachment where it is impossible

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to say whether it is or is not normally situated. We do not believe that it is advisable to make any great effort to feel the placenta if it is not readily palpable at the internal os. X-ray examination, either by means of a cystogram or with the soft tissue technique, frequently gives information of value, but this is not always true.

Keeping in mind these occasional difficulties in diagnosis, Table I gives the classification of our cases of antepartum hemorrhage for the years 1928 to 1944 inclusive. From this table we have omitted cases of excessive show which we decided, after delivery, were neither placenta previa nor accidental hemorrhage.

TABLE I. 1928 TO 1944 INCLUSIVE

		NO.	%
Total deliveries	16,115		
Antepartum hemorrhage		330	2.04
Placenta previa		191	1.19
Accidental hemorrhage		139	0.87
Maternal mortality		9	2.7
Infant mortality		131	39.6

Let us now consider the 191 cases of placenta previa. The usual classification of this condition is marginal, lateral, and central placenta previa, to which is sometimes added low implantation of the placenta. There is no uniformity of interpretation of this classification, and we have recently discarded it for one we think more practical. We classify our cases as complete or incomplete. The latter are subdivided into those where the placenta is palpable and those where it is not palpable. All classifications are relative as to the stage in labor when they are described. A placenta that entirely covers the internal os at the beginning of cervical dilatation may have a considerable area of membrane present beyond the edges of the placenta when the cervix is half or more dilated. Similarly, a placenta which may not be palpated before effacement of the cervix may be readily reached later in labor. As our new classification commenced only in 1933, Table II covers only 1933 to 1944. Of these, 31 were complete and 106 incomplete. Of the latter, 71 were palpable and 35 nonpalpable at the time of examination.

TABLE II. CLASSIFICATION OF PLACENTA PREVIA, 1933 TO 1944

Complete		31 (plus 23, 1928 to 1933)
Incomplete		106 (plus 31, 1928 to 1933)
Palpable	71	
Nonpalpable	35	

The results of treatment of the whole 191 cases during the 17 years are exhibited in Tables III, IV, V, and VI.

It is worthy of note that three patients had spontaneous deliveries without severe loss of blood and without maternal death in spite of the fact that the placenta completely covered the internal os at the time of examination. In one instance the placenta was expelled in front of the child's head. None of these patients, however, was more than six and one-half months pregnant.

TABLE III. COMPLETE PLACENTA PREVIA, 1928 TO 1944

TREATMENT	NUMBER	DEATHS	
Cesarean—classical	30	1	(intestinal obstruction)
—low	7		
—Porro	1		
Bag	4		
Version	8	1	
Spontaneous	3		
Undelivered	1	1	
	54	3	5.8%

TABLE IV. INCOMPLETE PLACENTA PREVIA, 1928 TO 1944

TREATMENT		NUMBER	DEATHS	
Medical induction		7		
Rupture of membranes or spontaneous labor		77		
Vaginal packing		2		
Bag		28		
Internal version		12	2	
External version		1		
Cesarean		10		
Classical	5			
Low	5			
		137	2	(1.46%)

In the 137 cases of placenta previa during 1933 to 1944, 69 had profuse bleeding from the start, and 68 had slight vaginal bleeding on one or more occasions. Information regarding the original bleeding in cases previous to 1933 is not available. Of the 68 cases which began with slight bleeding, 10 subsequently had profuse hemorrhage. Of these 68 cases, 9 were complete placenta previa and 59 were incomplete.

TABLE V. CASES BEGINNING WITH SLIGHT BLEEDING

Spontaneous	24	
Bag	13	
Section	17	
Version	8	(1 death)
Forceps	3	
Breech	1	
Packing	2	
	68	(1 death)

Table V shows the method of treatment of these 68 cases, from which it will be seen that slight bleeding as an original symptom does not determine the subsequent course of events. Seventeen of these patients, for instance, were treated by cesarean section. A practical problem in treatment is illustrated by this table. If a patient in the last trimester has slight painless bleeding it may or may not be due to placenta previa, but placenta previa should always be treated in a hospital. The patient, therefore, should be sent to the hospital before profuse bleeding has started. This will result in certain cases being sent to hospital who were having bleeding from the onset of labor without placenta previa, but no harm has been done, and those that really have placenta previa will be in the proper place for treatment.

TABLE VI. MATERNAL MORTALITY, PLACENTA PREVIA 1928 TO 1944

Total cases		191
Cesarean	1	
Undelivered, 20 minutes after admission	1	
Version	3	
	5	(2.6%)

Table VI is an analysis of our maternal mortality in the whole series of 191 cases. One death followed classical cesarean section and was due to intestinal obstruction which was relieved by operation, but the patient did not survive. The second patient died twenty minutes after admission before anything except a transfusion could be carried out. The other three deaths all followed internal version. One patient was discharged from the hospital on the seventeenth day, having had a normal temperature for a week. She returned two days later with a phlebitis and died suddenly four days after her second admission from pulmonary embolism. The other two patients both died of hemorrhage in spite of repeated transfusions. In both of these cases the hemorrhage had been severe before admission and was still continuing, and it was thought that version was the only method of immediately controlling the bleeding.

TABLE VII. STILLBIRTHS AND NEONATAL DEATHS IN PLACENTA PREVIA, 1928 TO 1944

TREATMENT	NUMBER	DEATHS	PER CENT
Expectant	86	18	19
Cesarean	44	8	18
Bag	31	15	48
Internal version	20	12	60
External version	1	1	100
Packing	2	2	100
	184	56	29.6

Table VII is an analysis of the fetal mortality when various methods of treatment were carried out. It will be seen that expectant treatment and cesarean section have by far the lowest fetal death rate. Those cases treated expectantly are the ones with the lesser degree of hemorrhage; many patients are already in labor and no further treatment becomes necessary during the course of labor. Cases treated by cesarean section in some instances had profuse bleeding, in other cases the operation was done because of complete placenta previa, and usually the patient was not in labor.

It has thus been shown that in our hands the treatment of placenta previa becomes a matter of judgment, and the factors that will influence the choice of method are: situation of the placenta, amount of hemorrhage, the parous condition of the patient, whether labor has or has not commenced and how it is progressing, duration of the pregnancy, presentation of the child and whether it is alive and viable. Any of these factors may be influenced by a combination of the others. We believe that a selective choice of treatment in a sufficiently large series of cases will show results to justify it. All cases of placenta previa should be treated in the hospital, and many of the emergencies could be avoided

if the significance of first bleeding were appreciated. The selective treatment of placenta previa necessitates a careful vaginal examination. This should not be done until the patient is in the hospital, has been completely prepared, and the operating room set up to carry out any procedure found necessary.

Accidental Hemorrhage

Some years ago we came to the conclusion that the incidence of cesarean section on our service was too great. Twenty-five years ago our incidence of section was between 2 per cent and 3 per cent. This subsequently rose until in one year it was just under 5 per cent. Subsequent study led us to the belief that two conditions—heart disease in pregnancy, and accidental hemorrhage—were the principal factors giving rise to this unnecessarily high incidence. As a result of that study, our incidence of cesarean section has dropped from a high of 4.9 per cent of all deliveries in one year to 1.93 per cent during the last three years.

TABLE VIII. ACCIDENTAL HEMORRHAGE

TREATMENT		NUMBER	DEATHS
Conservative (including rupture of the membranes and forceps)		120	1 (anuria)
Bag		5	1 (sepsis)
Version		2	
Cesarean		11	
Classical	7		1 (cardiac failure)
Porro	4		
Undelivered		1	1
		139	4 (2.9%)

Table VIII is an analysis of the treatment of 139 cases of accidental hemorrhage. In this series only 11 were treated by section, seven of them by classical section and four by Porro section. There was a total mortality of four, or 2.9 per cent. Of these four deaths one was due to anuria following conservative treatment, one was due to sepsis following the introduction of a bag, one was due to cardiac failure ten days after classical section, and the fourth patient died undelivered. We believe that the principal place for cesarean section in the treatment of accidental hemorrhage lies among patients at the two extremes of the condition. In a few mild cases, where the baby is alive and labor has not started, section may save a baby that might otherwise be lost. At the other extreme are the severe cases of uterine apoplexy in which the uterine wall is infiltrated with blood to such an extent that it is unlikely that it will improve sufficiently to expel the fetus. Even in these latter cases we would not think it advisable to operate upon a patient suffering from severe shock until transfusion and other methods of treatment have succeeded in restoring her general condition. Occasionally we have found that in the severe cases, where our first treatment is that of shock, by the time the shock is overcome the patient has already started in labor and may then proceed to a spontaneous delivery.

Table IX gives the fetal mortality. In all cases of accidental hemorrhage it is 60 per cent in our series, and we do not believe that this figure would be

TABLE IX. STILLBIRTHS AND NEONATAL DEATHS IN ACCIDENTAL HEMORRHAGE

TREATMENT	NUMBER	DEATHS	PER CENT
Cesarean	11	9	81
Other methods	128	73	57
	139	82	60

TABLE X. CESAREAN SECTION FOR ANTEPARTUM HEMORRHAGE, 1928 TO 1944

		NUMBER	DEATHS
Total deliveries	16,115		
Total sections	312		
Sections for placenta previa		44	1
Sections for accidental hemorrhage		11	1

markedly reduced by routine cesarean section. Indeed, we do not believe that such a procedure would reduce our mortality below 3 per cent.

Table X is an analysis of all our cesarean sections done for antepartum hemorrhage.

Summary

1. There are presented the results of selective treatment of 191 cases of placenta previa with a mortality of 2.6 per cent, and 139 cases of accidental hemorrhage with a mortality of 2.9 per cent.

2. These results, we believe, are comparable to those obtained by routine section in the treatment of these conditions and may avoid the additional risk of subsequent pregnancies by patients who have undergone cesarean section.

3. All cases of antepartum hemorrhage should be treated in the hospital if at all possible, and as the diagnosis cannot always be accurately made when the first bleeding is only slight, this will entail hospitalizing patients who may subsequently be proved to have neither placenta previa nor accidental hemorrhage.

4. In most emergencies of medical practice, where special skill is not available, conservative measures of treatment are usually in the best interests of the patient, but in placenta previa and probably in accidental hemorrhage, if skilled judgment is not available, radical method of treatment, namely cesarean section, is probably advisable.

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Discussion

DR. BENJAMIN P. WATSON.—Dr. Scott's conclusions are very much those that most of us have arrived at regarding this subject, and I have already stated my views on it, viz., that there are really only two methods of treating placenta previa: (1) by doing nothing, or by simply rupturing the membranes, and (2) cesarean section. Which of those two methods one adopts depends, as Dr. Scott says, on all the circumstances surrounding the particular case. I know that there are clinics in this country where a patient who comes in with bleeding in the last trimester of pregnancy is immediately taken to the operating room and a cesarean section performed. With that method of treatment I cannot agree any more than Dr. Scott. Placenta previa is one of those conditions in which obstetric judgment is required and obstetric experience counts.

In cases of separation of the normally situated placenta there is a trend, especially pronounced in Boston, for the more conservative treatment of those cases. I think a great many

of the cases which are subjected to cesarean section could very well deliver without it and probably with no great increase in the fetal mortality. In the severe cases, where the patient has sudden severe pain accompanied by shock, with a ligneous uterus, it is extremely difficult not to do a section because the patient looks in extremis, even after the primary treatment of the shock. Prompt delivery seems to be called for. It is just a question, however, whether, even in those cases, we would not get an equally good result by rupture of the membranes. We know when we open the abdomen in such a case that the uterus looks purplish-black in color, is extremely tense, is not undergoing any sort of rhythmic contraction; and yet, when the uterus is opened and the tension inside is relieved and the placenta and baby are removed, it goes into contraction, so that one may safely sew it up and leave it. The same result may be attained, even in such cases, if we had the courage simply to rupture the membranes, thus relieving the extreme tension and restoring the circulation in the uterine wall, so that the uterus would take on regular contractions and expel the baby and placenta per vaginam.

We have all noted in those cases when a section is done, that there is very little bleeding from the uterine wall and there is very little fresh blood loss from the placental site. So I think we should be more inclined to treat cases of accidental hemorrhage by more conservative means, namely, rupturing the membranes and allowing the uterus to expel its contents normally.

DR. EDWARD G. WATERS.—I do not believe it possible to outline a plan for management of abruptio placentae by a group appraisal of statistics. The parity of the patient and condition of the cervix are most important deciding factors. A separation of cases into mild and severe is almost imperative. The basic threat is death from shock and hemorrhage. The mild cases will respond to any sensible therapy. In the severe form one must decide whether, after combating shock and blood loss, it is safer to empty the uterus quickly by cesarean section or temporize in the hope that the patient will deliver vaginally without the additional risk of an abdominal operation. In arriving at the decision, medically remote experiences in similar cases possess only comparative value as against those managed more recently with freely used blood transfusions, blood plasma, and other antishock therapy, and modern forms of anesthesia.

In our clinic [The Margaret Hague Maternity] we believe that cesarean section fills an important place in treating severe abruptions. During the six years prior to 1943, we found in 414 abruptions of all types, that cesarean section was used in 72 patients, mostly with the severer form. There were only two deaths in the entire group, and *none* in the cesarean group. In view of such experiences, we believe that abruption is a real indication for cesarean section in many of the severe forms, especially in patients with "unprepared" cervix.

I have used one practical procedure in our clinic which may be of value to those who have not tried it. In some of our cases, section disclosed a severe degree of myometrial disruption, the uterus failed to respond to oxytocics, and the patient's condition precluded a hysterectomy. When faced with this formidable state of affairs, a rapid ligation of the uterine arteries proved lifesaving. The vessels are quickly and easily exposed by extending laterally the transverse vesico-uterine peritoneal incision and mass chromic catgut ligatures are passed around the artery on each side.

The major circulation and blood loss are immediately checked with a minimum of operative trauma. The anoxemia induced in the uterine musculature institutes a prompt and prolonged muscular contraction. The flabby uterus contracts, hemorrhage stops, and the patient is saved further and possibly fatal operative work.

DR. ALFRED C. BECK.—On our service at the Long Island College Hospital we are in accord to a large extent with the conclusions of Dr. Scott.

I do not agree with Dr. Watson in regard to the patient who is in a critical condition from accidental hemorrhage. That is not the case for surgery; that is the type of case which

is best treated conservatively. That is the case that we began to treat conservatively thirty years ago and we have not regretted our stand in those cases.

We do cesarean section for accidental hemorrhage in the early cases when the child is alive, largely in the interests of the child, but in these critical cases in shock with the loss of a lot of blood we prefer to treat the shock, rupture the membranes, and give pituitary extract, and in most of those cases they deliver and survive.

DR. HOWARD C. TAYLOR, JR.—This series of cases has been presented as if an identical policy had been pursued for seventeen years. I would like to ask Dr. Scott if that is a correct assumption, or whether he can describe some of the changes in viewpoint which have taken place during that period of time.

The title of his paper is "The Selective Treatment of Bleeding During the Last Trimester of Pregnancy." In his tables he emphasized particularly the many varieties of treatment used, especially in placenta previa. Dr. Watson, however, has concluded that there are only two methods of treating placenta previa—leaving it alone or resorting to cesarean section. I want to ask Dr. Scott whether, during the course of these seventeen years, his treatment has not tended to be less selective and more standardized.

In regard to premature separation of the placenta, I would like to ask whether the results particularly as regards the baby were not different when the cesarean rate was very low as compared with the previous policy in which it was very high. The infant mortality in those two sets of statistics, based on contrasted over-all policy, is the figure, we would like to know. It does not help to be told that in 9 out of 11 cesarean sections babies died because, as you saw, those were the bad cases. What we need to know is the total infant mortality rate with sections in 20 per cent of the cases as compared with the infant mortality rate when the cesarean section rate is high.

DR. HARVEY B. MATTHEWS.—I can subscribe to Dr. Scott's conclusions by and large except that I would like to put in a good word for the bag. Dr. Watson and I always differ on that and while I have no statistics on hand on the use of the bag, I know we have used it frequently in certain types of placenta previa, namely, marginal or partial, and have obtained good results, without undue infection following its use, with good control of hemorrhage, and successful delivery of the baby. So that while I agree with Dr. Watson that the two main principles or common methods of treatment of placenta previa are rupture of the membranes and cesarean section, yet there are some cases in which the bag can be used successfully, and those of us who were trained at the old Sloane Hospital under Dr. Voorhees and Dr. Cragin know that we can use bags successfully in certain cases.

In conclusion, I would like to say that while I would not want to see the bag discarded altogether in the treatment of placenta previa, we must agree that the two main methods of treatment are: let it alone, and cesarean section.

DR. RALPH L. BARRETT.—I have been a member of the Special Committee on Maternal Welfare in New York County for the past several years. From my own clinical experience and from the studies of this committee, I agree with Dr. Watson and must disagree with Dr. Matthews on the use of the bag in the treatment of placenta previa. Personally, I would be pleased if all bags were discarded in the treatment of this condition. Our statistics show that the bag has been the method of treatment in many of the deaths from placenta previa. Suitable cases, in which simple rupture of the membranes was the method of treatment selected, have done very well. The cases which have had an early cesarean under proper hospital facilities, has shown the lowest maternal mortality rate.

I do not think there is any in-between method of treatment. Either do an early cesarean section or, if the case is a partial previa in a multiparous woman with a partially dilated cervix, simply rupture the membranes and await delivery.

Dr. Scott's paper shows that the majority of deaths in his series occurred in those cases where bag or versions of breech extraction was the method of treatment. It is this group of

cases that showed the highest mortality rate both for mother and baby. In general, his results as outlined in this paper were excellent, but I wish he would drop the bag and version in the treatment of placenta previa.

DR. SCOTT (closing).—I quite agree with Dr. Watson that in a case of accidental hemorrhage with a hard, distended, ligneous uterus the membranes should always be ruptured as soon as possible.

Dr. Taylor's question was much to the point. There has been a change in our practice in seventeen years, but probably not so much as he might think. I have pointed out that our incidence of section rose from about 2.5 per cent to 5 per cent and is again back to 1.9 per cent of all deliveries. There has been some slight change in our management of both types of antepartum hemorrhage. Such change is inevitable where judgment is the basis of procedure. Probably my judgment will be influenced to some extent by the discussion we have had tonight. In hospital practice, packing certainly should disappear, and version probably should do so. The latter may have a place in practice remote from hospitals. In the use of the bag there has been some change, and we certainly use it less frequently than we did fifteen years ago. We still think, however, that it has a place in properly selected cases, and I should hate to see it not available on our service.

Dr. Waters' remarks are worthy of consideration, and one would have liked a more detailed analysis of all these cases, but this was impossible in the time at my disposal. As I pointed out, the question of when to do a section in cases of severe abruptio placentae is a matter of judgment, and in a given case his judgment might be different from mine. Over the period under discussion we have become much more conservative, and with increasing experience we have courage to treat conservatively cases that previously would have had a section. There has not been a cesarean section for accidental hemorrhage during the past three years, and our mortality rate has not gone up.

A HISTOLOGIC STUDY OF THE EFFECT OF IRRADIATION ON ADENOCARCINOMA OF THE ENDOMETRIUM

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THE use of irradiation in the therapy of adenocarcinoma of the endometrium has attracted widespread attention. The early results of radium therapy in this disease were not encouraging, due perhaps to the fact that inadequate dosage and distribution were used. The recurrence of symptoms in the presence of active tumor after irradiation may occur only after long intervals so that hastily drawn conclusions as to the effectiveness of the irradiation are unjustified. Accordingly, long periods of time must elapse after therapy before results can be assessed and as yet very few reports satisfy this requirement. Numerous preliminary reports are available in the literature regarding the effectiveness of radium or radon alone. Especially notable are the reports from the Radiumhemmet in Stockholm. In this country more attention has been directed toward the combination of irradiation and surgery, in the hope of improving the cure rates obtainable by surgery alone. Another factor contributing to the increased use of radiotherapy has been the need for some form of at least palliative therapy in those patients who are unsuitable for the surgical attack either because of known extension of the tumor or because of the presence of some contraindication to surgery such as diabetes, heart disease, or obesity. Most of the evaluation of radium therapy has been on the basis of clinical results in terms of five- or ten-year cure rates, or in increase in survival rates, and little attention has been paid to the correlation of these results with histologic findings.

X-ray irradiation has also been used in the treatment of this disease. In some instances this has been used alone and in others in conjunction with radium irradiation. A third group has been treated by a combination of x-radiation and surgical therapy. Again study has been directed toward clinical cure and survival rates among patients subjected to these types of therapy, as compared with those treated by surgery alone. Reports dealing with the presence of viable carcinoma cells in operative specimens are extremely few.

Since it is likely that complete eradication of the tumor by whatever means of therapy is employed is essential to the production of cure, it seems logical to examine the effect of irradiation therapy on the carcinomatous tissue. The purpose of this paper is to present a series of fifty-three cases of adenocarcinoma of the body of the uterus, which were proved by examination of tissue obtained by curettage, and which have been treated either by a combination of radium application and surgery, or by radium, deep x-ray, and surgery. The material for histologic study was obtained by subjecting the patients to panhysterectomy with bilateral salpingo-oophorectomy at approximately five weeks after the completion of the irradiation therapy. The gross material has been carefully restudied and multiple blocks of tissue from each uterus were sectioned.

Few similar reports are found in the literature. Healy and Cutler,[1] reported on a series of patients treated by many combinations of irradiation therapy and surgery. They noted a few cases in which there was no demonstrable tumor in the uterus, but did not state how extensively the uterus was searched. The dosages of radium and x-ray employed, as well as the interval between this therapy and surgery, varied considerably. It was concluded that the well-differentiated tumor was most readily eradicated. Healy,[2] in a general report on irradiation therapy in malignant disease of the female generative tract, stated that (in adenocarcinoma of the endometrium) "very little viable carcinoma, and in more than half of the cases no carcinoma at all, could be found in the uterus on microscopic examination after its removal." The dosages employed are not stated, nor is there any statement as to the thoroughness of the search for the tumor. Operation was done in these cases four to six weeks after the completion of the irradiation. Arneson[4] reported on ten cases treated by the insertion of two or more capsules of radium in tandem into the cavity of the uterus, followed by operation in from two to eight months. In four of the six cases which received more than 3,000 mg. hr. of radium irradiation, no carcinoma was demonstrable. Active tumor was found in every case which received a smaller dose. Again the extent of the search for tumor was not stated. E. Marquis[5] reported persistent carcinoma in 21 of 29 uteri removed six weeks after being subjected to 55 to 60 mc. destroyed of radium (7,260 to 7,920 mg. hr.). He did not describe the method of application of the radium, nor did he indicate how extensive was the search for tumor in the excised specimens. Healy and Brown[6] searched the uteri of 75 women with adenocarcinoma of the body of the uterus. These had been removed six to eight weeks following irradiation therapy. Of these, six which were treated with deep x-ray alone all showed residual carcinoma. The remaining 69 patients were all treated with radon, therapy having been given in each case by means of two or three capsules in tandem, each capsule being 15 mm. in length, and the combined capsules having a strength of from 75 to 150 millicuries. Three of 24 cases (12 per cent) treated with 1,200 to 1,700 mc. hr. showed complete regression of the tumor, 13 of 25 cases (52 per cent) given 3,000 to 3,300 mc. hr. showed complete regression, as did 12 of 20 cases (60 per cent) given 3,400 to 4,000 millicurie hours. They stated that "a careful microscopic examination" was done on these uteri. Corscaden[7] in his discussion of this paper stated that only 8 of 21 patients treated by him showed no carcinoma on examination of the uterus after irradiation and operation, but he gave no details of therapy or of search.

In the course of his description of a hysterostat for intrauterine application of radium and of its use in eight patients, Friedman[8] reported eradication of the tumor in seven. All of these patients received at least 4,000 mg. hr. of radium irradiation. He did not give any details as to the thoroughness of the search for residual tumor in these cases, in which the uteri were removed four to six weeks after irradiation therapy. Smith[9] reported 24 cases of adenocarcinoma of the uterus treated with 2,400 to 3,600 mg. hr. of radium irradiation delivered from tandem capsules. A few of these patients also received 1,600 r. (point of measurement not given) by deep x-ray. When the uteri were removed four to seven weeks later, only four were completely free of tumor. The extent of the search was not stated.

The findings in a series of 46 patients treated with radon in single applicators on whom hysterectomy was carried out four to six weeks later were reported by Donovan and Warren.[12] The uteri of only five of these patients were free of carcinoma on routine examination of representative areas. The dosages employed in these cases varied widely. One patient received only 1,700 to 2,000 mc. hr., but her uterus failed to show residual carcinoma. Five of six receiving 2,000 to 2,500 mc. hr. showed tumor remaining, as did all of six receiving 2,500 to 3,000 mc. hr., 17 of 18 receiving 3,000 to 3,500, 11 of 13 receiving 3,500 to 4,000, and two receiving 4,000 to 4,500 millicurie hours. Schmitz, Sheehan, and Towne[13] published in 1943 a report on 77 cases of adenocarcinoma of the corpus uteri. Among these were eleven in which the uterus was removed following irradiation. In five who received what they term "adequate" therapy, no carcinoma was found, while in the remaining six which received less than adequate therapy, grossly recognizable carcinoma was present in every instance. Four patients among seven others receiving adequate therapy underwent subsequent curettage. In none of these was carcinomatous tissue demonstrable. However, one of these patients died

of metastasis within a year. Carcinoma was found in three of six patients who had had inadequate therapy and subsequent curettage. These authors defined adequate therapy as 6,000 mg. hr. of radium irradiation given in three doses of 2,000 mg. hr. each at intervals of from seven to eight days, application being made in the Y-capsule described by Schmitz and Schmitz.[3] This is followed by deep x-ray therapy. "The dose attained within the pelvis after twenty-eight days was 4,000 roentgens, with backscatter." Operation was done at intervals varying from three to eight months after irradiation in the five patients in whom no residual tumor was demonstrable. In these, the entire endometrium was blocked, and numerous sections were cut from each block, in the attempt to find tumor tissue. Of the remainder in which some type of surgical procedure was carried out in addition to the irradiation, the interval between these varied considerably.

Another report appearing in 1943, that of Scheffey, Thudium, and Farell,[14] included thirty cases of adenocarcinoma of the uterine fundus in which the combined therapy had been given. Fifteen of these thirty showed no tumor in the specimen removed eight to ten weeks after completion of irradiation. Of the nine patients who received 4,000 to 5,000 mg. hr. there were only two whose uteri contained demonstrable tumor. The method of radium application here was two or three 50 mg. capsules in tandem, left in position long enough to deliver the desired dose. No statement was made as to the thoroughness of the search for tumor in these specimens.

Examination of these results brings out a number of significant points. In the first place there is little agreement as to what constitutes adequate dosage in the irradiation therapy of adenocarcinoma of the corpus uteri. The variations are considerable, and perusal of other reports concerned with the treatment of this neoplasm by means of radium or radon supplies additional evidence of this. Success is not likely to be achieved where inadequate dosage has been employed. Better results have been obtained when at least 4,000 mg. hr. of radium irradiation or its equivalent in millicurie hours where radon has been used have been given. Wide variation is noted as well in the methods of application.

The majority of those quoted above[4, 6, 9, 12, 14] used either single applicators or capsules in tandem, while Friedman[8] used a hysterostat and Schmitz and co-workers[13] used a Y-applicator. Irradiation may be expected to be ineffective if either distribution or dosage is uncontrolled. Heyman[10] pointed to this fact in stating that the results at the Radiumhemmet had been improved when multiple capsules were packed into the cavity of the uterus instead of the single tandem applicator. Friedman[8] showed by the use of an ingenious series of models that the ordinary methods of application fail to deliver adequate tumor dosage to all parts of the corpus. His hysterostat was designed to overcome this and to overcome as well the difficulties in delivering adequate dosage in those uteri whose cavities are distorted by the presence of other pathology such as myomas. Since the latter are frequently found in the presence of adenocarcinoma of the endometrium, and since these may on occasion markedly distort the uterine cavity, the control of distribution of dosage is essential.

X-ray therapy was used either alone or in conjunction with radium by the authors of four of these papers.[1, 5, 8, 13] Here again there was little agreement as to dosage requirements. The measurement of the amount of irradiation energy delivered to the tumor area received attention in only one paper. Schmitz and co-workers[13] reported a calculated depth dose. The others contented themselves with mentioning the use of x-ray or stating that a given number of roentgens were delivered without reference to the point at which the measurement was made. It may be concluded that the value of deep x-ray in the therapy of adenocarcinoma of the endometrium is not yet proved.

Author's Study

The present study is based upon 53 patients with adenocarcinoma of the body of the uterus who were treated for this condition at the University of

Minnesota Hospitals during the years 1939 to 1943, inclusive. All had both irradiation therapy and surgery. With one exception all the patients studied had their complete therapy in this institution. One patient received 3,600 mg. hr. of radium irradiation elsewhere. This was delivered from three capsules in tandem. She was transferred here to receive 219 per cent ESD (2,190 tissue roentgens) measured at the uterus over twenty-eight days and for subsequent total hysterectomy. All patients received radium irradiation prior to surgery. In seven this was given from two or three capsules arranged in tandem in a single long applicator, while in the remaining cases the radium was arranged in a jointed tandem applicator to be described below. Twenty-three patients had deep x-ray therapy prior to operation as well. Twelve of these received more than 250 per cent ESD to the uterus as above (100 per cent ESD equalling 1,000 tissue roentgens), over about four weeks, and eleven received a lesser amount. This was discontinued as a routine procedure on July 1, 1941, and since then only preoperative radium irradiation has been used.

In the instances where the straight tandem was employed, the amounts of therapy were as follows: two cases, 2,000 mg. hr. of radium irradiation; one case, 2,400 mg. hr.; one case, 2,500 mg. hr.; one case, 3,600 mg. hr. plus 219 per cent ESD of deep x-ray therapy; one case, 4,000 mg. hr. plus 200 per cent ESD; and one case, 4,900 mg. hr. plus 155 per cent ESD. Table I gives the amounts of therapy in those patients treated with the jointed tandem applicator. Those patients who received it were given deep x-ray therapy first, usually over the course of about four weeks, and this was immediately followed by radium application. When the full dose of radium irradiaton had been received, the patient was discharged from the hospital, to be readmitted about four weeks later for operation, total hysterectomy and bilateral salpingo-oophorectomy being carried out. In one case there was a three-year interval between the completion of the irradiation and operation. It had been planned originally to treat this patient with irradiation alone, since she was quite obese and had diabetes and chronic cholecystitis, but the appearance of vaginal bleeding prompted eventual hysterectomy. In another patient the interval was three months, as the patient had hyperthyroidism, necessitating subtotal thyroidectomy. In all other instances operation followed the completion of irradiation therapy by 4 to 8 weeks.

TABLE I. THERAPY IN 46 PATIENTS TREATED WITH JOINTED TANDEM APPLICATOR

RADIUM (MG. HR.) GIVEN OVER 100 HR.	DEEP X-RAY (IN ESD TO UTERUS OVER 4 WEEKS)			TOTALS
	NONE	250% OR MORE	LESS THAN 250%	
4,500 or more	23	10	7	40
Less than 4,500	3	2	1	6
Totals	26	12	8	46

In forty-six cases a jointed tandem applicator was used. This was designed to overcome the objections to straight tandem applicators and to permit of easy application. The uterine cavity is directly measured. Five capsules with platinum walls 1 mm. in thickness contain the radium element and are placed in series in a long piece of rubber tubing, the capsules being fixed in position by firmly ligating the tubing between adjacent capsules. The resulting triangle has two capsules on each side and one at the base, and must accurately fit the uterine cavity. The applicator will bend to some degree to accommodate itself to varying shapes of the cavity. As well, the length of each capsule within the tandem can be varied to suit the depth of the cavity and the width of the fundus. For smaller uteri a three-capsule triangle is used. In the usual five-capsule setup, 45 to 50 milligrams of radium are applied over the course of 100 hours to deliver 4,500 to 5,000 mg. hr. of radium irradiation. The practice has

been to place in succession in the tubing capsules containing 7, 10, 15, 10, and 8 mg. of radium, respectively. The combined effects of these when formed into a triangle will produce a diffuse dose to the cavity. In applying the radium, the rubber tube is bent double between the second and third capsules and in this shape is slipped into the cavity. Preliminary dilatation of the cervix is carried out if necessary. When the fundus is reached the shorter arm of the applicator is held stationary while the longer arm is introduced more deeply. This has the effect of causing the middle capsule to come to lie transversely across the fundus. In most instances the introduction of this applicator is a rapid and simple matter.

The uteri were removed at an arbitrary four to five weeks after the completion of the irradiation, and immediately after operation routine sections were made of any suspicious areas. When there was no gross evidence of carcinoma, sections were taken from two or three areas in the fundus and cervix. These have been reviewed, and those uteri which were apparently free of carcinoma at the time of the original examination have been re-examined. In order to make sure that no carcinoma was overlooked, the entire endometrium, together with the musculature underlying it to a depth of 0.7 to 1.0 cm., was removed, and sections were made at intervals of not more than 3 mm. at right angles to the surface. It was felt that there was very little chance of carcinoma escaping detection by this method.

TABLE II. RESIDUAL CARCINOMA

AMOUNT OF X-RAY	4,500 OR MORE MG. HR. RADIUM IRRADIATION			LESS THAN 4,500 MG. HR. RADIUM IRRADIATION		
	NO.	CARCINOMA PRESENT	%	NO.	CARCINOMA PRESENT	%
None	23	13	56.5	3	2	66.7
250% ESD or more	10	4	40.0	2	1	50.0
Less than 250% ESD	7	3	42.8	1	1	100.0
Totals	40	20	50.0	6	4	66.7

In 27 of the total of 53 uteri (50.9 per cent) residual carcinoma was found. Carcinoma which was deep in the muscular wall but showed none at the surface of the endometrial cavity was found in 19. Of these 19, 17 were discovered on routine section, while the remaining two were found during the course of the present study with complete sectioning of the endometrial cavity surfaces. In these two there was no surface carcinoma, but extensive tumor growth was seen in the myometrium. Three of the uteri showed carcinoma both at the surface and in the muscle, while in five, surface tumor was present without invasion of the muscle being evident.

In the seven patients treated with a single straight tandem applicator, there were three instances of residual carcinoma. The incidence was 42.8 per cent. Two of the cases received only 2,000 mg. hr. of radium irradiation, while the third received 4,900 mg. hr., together with 155 per cent ESD of x-radiation at depth. In all these cases the tumor was discovered on routine examination.

Forty-six of the uteri had been treated by other means than the straight tandem radium applicator. Of these, 24 were found to have apparently viable residual carcinoma, and in 22 it was discovered on routine examination of the operative specimen. Forty of the 46 patients received at least 4,500 mg. hr. of radium irradiation, the great majority receiving at least 4,900 milligram hours. Residual carcinoma was found in 20, or 50 per cent. X-ray therapy was not given to 23 of these patients, and in 13 of this group, an incidence of 56.5 per cent, residual tumor was present. Seven of the remaining 17 who received deep x-ray therapy as well as radium irradiation showed residual carcinoma in the excised uteri, with an incidence of 41.2 per cent. The six remaining patients in the series received less than 4,500 mg. hr., and of these four had residual carcinoma. These results are summarized in Table II.

The microscopic appearances of the sections taken from the uteri of these patients showed wide individual variations. Three rather distinct pictures were seen in the uteri where there was no viable carcinoma, and any combination of the three could be seen in a given instance, although usually one picture predominated. A few of the uteri showed complete necrosis of the

endometrial surface, and not infrequently this change extended into the musculature. For a depth of several millimeters the tissue was converted into a homogeneous pink-staining mass. Cell boundaries were entirely lost, and a few fragments of material staining intensely with hematoxylin were all that remained of the nuclei. Usually a zone of small round cells, polymorphonuclear leucocytes, and hemorrhage, with some formation of granulation tissue, marked the boundary between the necrotic area and the surviving muscle. The irregularity of the boundary zone in some places suggested the possibility that infarction, as well as cell death as a direct result of the radium, may have played a part in the production of the marked necrosis.

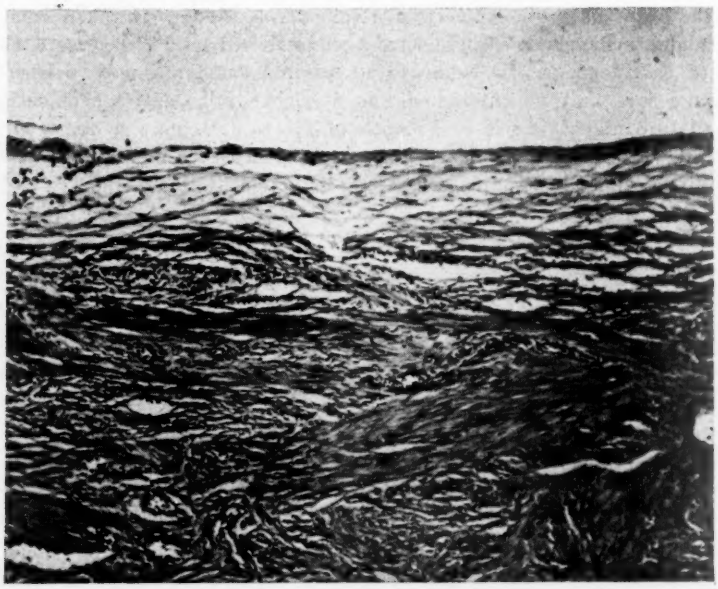

Fig. 1.—(×100). Endometrial surface of uterus after irradiation, showing complete eradication of tumor tissue. See description in text.

In the majority of instances where residual tumor could not be demonstrated, the microscopic appearance was that of Fig. 1. The lining of the endometrial cavity has been changed to a zone of rather loose granulation tissue in which are seen a few small blood vessels. At the surface the tissue is denser, and occasional swollen, finely granular surface epithelial cells are seen. Immediately beneath the zone of granulation the myometrium begins. It appears relatively unaffected, is perhaps slightly atrophic, and there are only scattered small round cells. This section was taken from the uterus of a 51-year-old white woman which was removed four and one-half weeks after the completion of 4,900 mg. hr. of radium irradiation, given because of a proved adenocarcinoma of the endometrium.

Fig. 2 illustrates a section taken from the uterus of a 46-year-old white woman four and one-half weeks after completion of 4,900 mg. hr. of radium irradiation, and is typical of the next most frequent microscopic picture. Here again there is a zone of loose granulation tissue quite similar to that in Fig. 1. In addition, however, a number of irregular gland spaces are seen. These are lined by distorted epithelial cells whose cytoplasm is granular, more than usually eosinophilic, and slightly vacuolated. Nuclei are moderately pyknotic. It is not possible to say whether these are endometrial glands or represent damaged carcinoma, but it is felt that the former is more likely from the general pattern. Scattered small round cells are also seen.

In those instances where viable tumor was present the pattern was entirely characteristic of adenocarcinoma. Fig. 3 shows one such area. This section was taken from the uterus of a 53-year-old woman removed six weeks after the completion of 4,900 mg. hr. of radium irradia-

Fig. 2.—(×100). Lining of endometrial cavity after irradiation showing cleftlike glandular spaces lined by columnar epithelium. For description, see text.

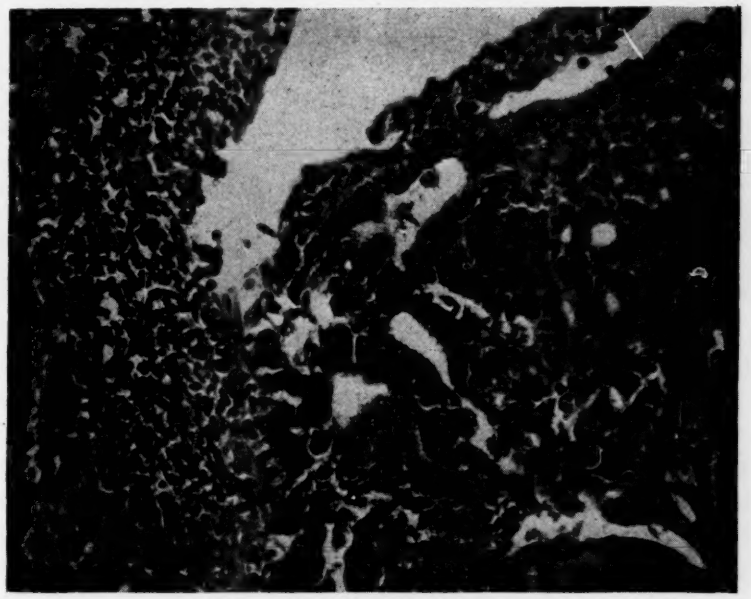

Fig. 3.—(×270). Lining of endometrial cavity after irradiation showing relatively little effect on tumor tissue. See text for description.

tion. Viable tumor at the endometrial surface, and as well the base and stalk of a polypoid growth of tumor, are seen. There is some evidence of irradiation effect upon the tumor cells, but it is not marked. Round cells are grouped beneath the tumor, but are probably the natural concomitant of the latter rather than evidence of irradiation effect. Other areas in this section showed greater damage to the tumor, amounting to complete destruction on occasion, but they were distributed very irregularly. This general picture was typical of the instances where surface tumor remained. Undamaged tumor was always present to some degree, frequently in close apposition to areas of advanced degeneration. It must be pointed out, however, that some areas of complete necrosis or destruction of the surface tumor were always seen, and this is in contrast to the picture when only tumor in the depth of the muscle remained. In Fig. 4, a portion of a section taken from the uterus of a 74-year-old woman, removed about five weeks after 125 per cent ESD of deep x-ray irradiation and 4,500 mg. hr. of radium irradiation had been given, tumor tissue is seen deep in the muscular wall of the uterus. There is little evidence of irradiation effect on the tumor cells. A few are slightly swollen and granular, but the majority are undamaged.

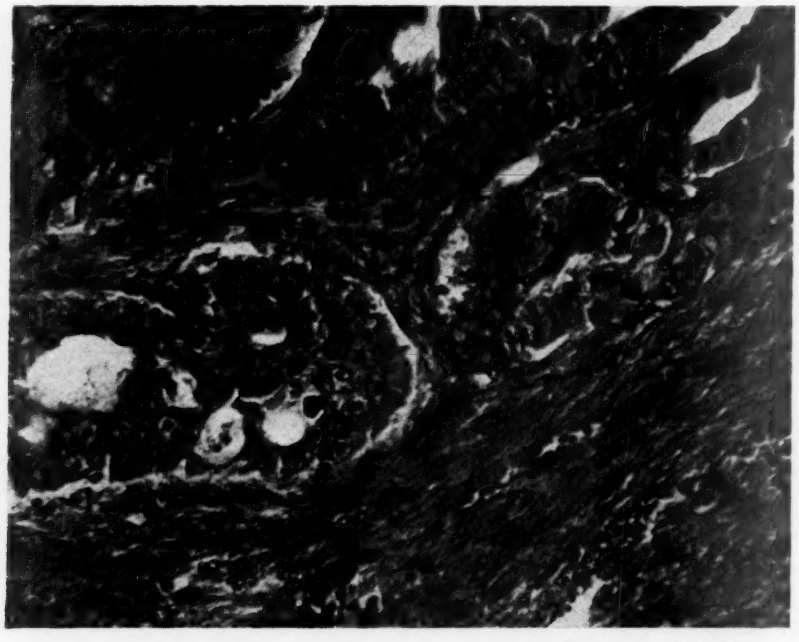

Fig. 4.—(×270). Section of uterine wall taken postirradiation. Viable tumor seen in the muscle. Description in text.

Discussion

It is apparent that eradication of adenocarcinoma of the body of the uterus is not attainable by these methods of irradiation therapy. The fact that residual carcinoma was found to be present in the uteri of a high percentage of these patients, even in the most heavily treated group, makes it quite clear that surgery must continue to have a place in the attack on this disease. This concept is borne out by the reports quoted earlier which showed that residual carcinoma was absent only occasionally after irradiation. In the great majority of the reported studies there was a fairly high incidence of carcinoma present following various forms of irradiation therapy.

Several factors must be taken into account in assessing the value of irradiation treatment of any type in eliminating carcinoma. In the first place one must of course consider the possibility that the entire growth may have been removed at the time of curettage. This might conceivably occur when the tumor is revealed quite early in its course before invasion of the uterine musculature has taken place, the tumor being limited to a small area on the endometrial surface. One might suspect this situation when not all of the material obtained at curettage is carcinomatous.

Second, the total amount of therapy must be considered. One cannot expect complete elimination of the neoplasm where inadequate amounts have been employed in spite of the fact that in occasional instances cure will apparently be produced by small amounts. It has already been emphasized that the distribution of radiation energy must be such as to deliver the maximum dosage possible to the tumor, and it felt that the applicator described in this paper has been successful in effecting this in this small series. The uteri of 12 of the 46 patients thus treated showed distortion of the outline of the endometrial cavity because of myomas or adenomyosis uteri interna. Exactly half of them contained residual tumor, and in every instance it was found deep in the musculature, no tumor being seen at the surface. Among the uteri the outline of whose cavity was unchanged the incidence of residual carcinoma was slightly over 50 per cent, and in seven of these, surface carcinoma was present. The persistence of viable tumor deep in the muscle might be a consequence of inadequate irradiation of the tissues at even small distances from the source of energy. Arneson and Hauptman[11] have pointed this out in connection with the use of straight tandem applicators, and have shown greater effect on both surface and deep tumor when the distribution of energy is improved.

Other factors are more likely to account for this persistence of tumor in the depth of the muscle after irradiation. Tumor is seen to persist in the musculature even when it is close to the endometrial surface. No scarred areas have been found in the musculature after irradiation as one might expect if tumor had been present and been destroyed. In other words, no evidence has been obtained from this study to suggest that tumor which has invaded the muscle to lie beneath the surface is ever destroyed by irradiation. On the other hand, it has been clearly demonstrated that tumor in the musculature of the uterus often does escape destruction in spite of maximum irradiation. The clinical significance of this is obvious.

Finally, the role of deep x-ray therapy must be considered. The short series reported here seems to indicate that the combination of adequate amounts of radium irradiation plus adequate amounts of deep x-ray therapy should produce results, as far as the elimination of tumor tissue is concerned, which might be expected to better those produced after the use of radium alone. It must be emphasized, however, that the number of patients so treated is not great enough to enable one to assert that the addition of x-ray to the plan of therapy is necessarily worth while. The application of the Chi-square formula indicates that the difference noted in this series is not statistically significant. An increase in the frequency of complications following the use of x-ray therapy seem to be

out of proportion to the advantages obtained. This will be reported in detail elsewhere. Undoubtedly the problem deserves much further study before an authoritative answer can be given.

Summary and Conclusions

1. The literature dealing with the detection of residual tumor and its frequency in adenocarcinoma of the endometrium treated with radium, radon, and deep x-ray therapy has been reviewed. These reports show persistence of apparently viable tumor in from 12.5 per cent to 89 per cent. There was wide variation in the amount of therapy given, in the type of radium or radon applicators used, in the intervals between irradiation therapy and operation, and in the thoroughness of the search for residual tumor in the operative specimens.

2. The incidence of residual tumor in the uteri of the 53 patients studied in this paper was 50.9 per cent. All of these patients had intrauterine radium application; 23 had deep x-ray therapy as well. In a small series where x-ray was employed in adequate dosage together with radium irradiation, the incidence of residual tumor fell to 40 per cent, while in a longer series where radium alone was used the incidence was 56.5 per cent.

3. An applicator designed to overcome the effect of variations in size and shape of the uterine cavity is described. It was used in forty-six of the fifty-three cases.

4. In the majority of instances where residual carcinoma was found, it was seen in the musculature of the uterus. The significance of this is discussed.

5. In view of the fact that tumor persisted after irradiation in a high percentage of cases, and especially in view of its frequency in the myometrium, it is concluded that surgical attack must be considered to be the essential feature of curative therapy in the treatment of adenocarcinoma of the corpus uteri. It is still possible that preliminary irradiation may be useful as additional therapy or as palliation.

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THE MANAGEMENT AND TREATMENT OF THE LATE TOXEMIAS OF PREGNANCY*

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BY "toxemia of pregnancy" is understood a disturbance occurring during or in connection with pregnancy, consisting of a variety of syndromes, the most constant factors of which are hypertension, proteinuria, and edema. To these may be added a variety of renal, gastrointestinal and nervous symptoms, the most important of the last being convulsions and coma. The disease is most protean in its clinical manifestations. Yet there is no general agreement as to whether there is, in the words of Goodall, "one toxemia of pregnancy," the multiform manifestations depending on one as yet undetermined specific cause, as typhoid fever and syphilis in all their varying clinical pictures depend on their respective specific causative organisms; or whether, as Dieckmann and many others believe, a number of different causes may operate in the pregnant woman, to give rise to a more or less similar group of manifestations.

In an attempt to standardize present concepts of pathologic and symptomatic variations into an admittedly imperfect but at least widely acceptable and workable system of nomenclature, the American Committee on Maternal Welfare adopted the now familiar system of nomenclature which is currently in more or less general use.

Group A. Disease not peculiar to pregnancy:
- I. Hypertensive disease (hypertensive cardiovascular disease)
  - a. Benign (essential), mild, severe
  - b. Malignant
- II. Renal disease
  - a. Chronic vascular nephritis or nephrosclerosis
  - b. Glomerulonephritis
    - (1) Acute
    - (2) Chronic
  - c. Nephrosis
    - (1) Acute
    - (2) Chronic
  - d. Other forms of severe renal disease

Group B. Disease dependent on or peculiar to pregnancy:
- I. Pre-eclampsia
  - a. Mild
  - b. Severe
- II. Eclampsia
  - a. Convulsive
  - b. Nonconvulsive (that is, coma with findings at necropsy typical of eclampsia)

Group C. Vomiting of pregnancy

Group D. Unclassified toxemias

*Presented by Dr. Cosgrove before The Hamilton Academy of Medicine, Hamilton, Ontario, Dec. 5, 1944, and The Toronto Academy of Medicine, Toronto, Ontario, March 6, 1945.

Pre-eclampsia.—Mild: "Mild pre-eclampsia" is the term applied to that condition which may arise during pregnancy, almost always after the twenty-fourth week, characterized by a moderate rise in systolic blood pressure to about 140 to 160, and a diastolic blood pressure of 90 to 100 mm. Hg. The urine contains less than 0.6 Gm. of albumin per 100 c.c. and the edema is usually slight and rarely may be absent; usually no changes are demonstrable in the retinal arteries.

Severe: A condition, which usually becomes evident after the twenty-fourth week of pregnancy, is characterized by a sustained systolic blood pressure of more than 160 and usually a diastolic blood pressure more than 110 mm. Hg, usually accompanied by the passage of more than 0.6 Gm. of albumin per 100 c.c. of urine. The edema is severe in most cases. Usually hypertensive changes may be observed in the retinal arteries.

As already stated, this system of nomenclature is not completely satisfactory, as its proponents very clearly recognize, but it is capable of use as a serviceable medium of thought exchange. The destructive criticism of it contributes nothing to the useful potentialities of helpful interchange of experience. Such interchange of experience, however, is necessary for progress in our understanding and handling of the disease. This nomenclature by its wide adoption provides a medium of such commerce which, granting any of its imperfections, is capable of being just as useful as is the far from puristic "pidgin English" of the Orient, in material barter and exchange.

The pathology of the disease is as various as its symptomatology. Any of the important viscera may partake more or less extensively of the pathologic changes. Among the more constant pathologies are those involving the liver, the kidneys, the brain, the vascular system, the theart, the adrenals, the pituitary, and the organs of special sense, notably the eyes. Yet there is no absolutely pathognomonic picture. There is no single lesion which will permit the pathologist, without reference to the clinical history of the case, to say on the one hand, "This woman certainly *had* eclampsia," or on the other hand, "This woman certainly *did not have* eclampsia."

Ideas of pathogenesis are of course closely linked with shifting conceptions of pathology. At the very dawn of the modern era of physiologic chemistry, the constant and frequently severe degree of proteinuria led observers to consider toxemia as primarily a form of nephritis, or uremia. The variation in severity of the renal lesions, however, even in clinically most severe and fatal cases, forced the abandonment of this idea. About the turn of the century, attention was critically focused on the frequent and significant changes in the liver. At that time observers *did* believe that the hepatic changes were of one pattern that was pathognomonic of the disease. Extreme variations in the type and severity of liver pathology, however, eventually in turn forced abandonment of belief in an absolutely pathognomonic pattern in this organ, while at the same time important pathologies of other organs obtruded their significance. Most recently there has been a recognition of definite functional and structural changes in the vascular system, particularly the capillaries and arterioles. This seems to be the common denominator present in all observed visceral pathologies, and of their hemorrhagic components. This has led to the acceptance, by many astute observers, of these changes in the blood-vascular system as the most significant and universal pathologic tendency.

The search for an ultimate pathogenic basis of the disease, apart from its broad association with pregnancy itself, has been assiduous and painstaking for nearly a century. The term, "toxemia," of course connotes some specific poison or toxin circulating in the blood, comparable to bacterial toxins of certain specific diseases, which are responsible for the clinical manifestations of those diseases. Hence, physiologic chemists and bacteriologists alike have arduously sought the existence and identity of such an agent, completely without success, so that up to the present time the very term toxemia cannot be logically justified. The association of the disease with the presence within the maternal organism of a living conceptus has of course concentrated the search for such a pathogenic factor to a very large extent on the products of fetal and placental metabolism. Besides, all the other fields of physiologic disturbance, such as the endocrinopathies, dietary and nutritional variations, the allergic states, have been fine combed in vain.

Therefore, in regard to the pathogenesis of eclampsia, we even today might properly paraphrase the immortal Omar to the effect that,

> "Myself when not-so-young did eagerly peruse,
> Doctor and doctor and heard great argument,
> About it and about, but evermore came out
> By the same door wherein I went."

Because in 1883, Barnes said, "There has been going on a most active inquiry as to the etiology of puerperal convulsions, with . . . frequent modification of theory; but, even at the present day science has not settled the question." Many years later, Whitridge Williams said, "It is apparent that the cause of eclampsia has not yet been discovered." To neither of these statements am I able today to add one single word.

Lacking then a guide in the form of any established knowledge of etiology and pathogenicity, the management and treatment of the late toxemias of pregnancy remain on exactly the same basis upon which our fathers established it It presents three phases: (1) prophylaxis; (2) the treatment of symptoms; (3) the termination of the pregnancy. The only changes that the years have seen have been some improvement in the average level of medical awareness of the diagnosis and treatment potentialities of the earlier stages. By this I mean that the leading writers of two generations ago expressed a knowledge of the principles of treatment which would be, at least broadly, entirely acceptable today. It is very certain, however, that this knowledge was not at that time so thoroughly and usefully disseminated among the rank and file of the profession as is the thought of the leading authorities of today. Hence, far fewer victims of the disease derived the benefit of principles which had already been well established.

All of this is interestingly shown in a comparative table (Table I).

The present practice of our Clinic will be briefly summarized. Details will of course vary with the individual case, and to some extent with the three service chiefs, equal in clinical authority, who are responsible for the work.

TABLE I

IN 1880	IN 1944
I. Prophylaxis Stressed	
It consists of frequent contact with the patient; the regulation of her general hygiene and diet; watching her for morbid manifestations	
(1) in general symptoms, especially weight gain and edema	
(2) in urinary anomalies	
By chemical and microscopic findings	Plus a variety of renal function tests
(3) in blood pressure variations	
By sphygmograph, available to but few observers	By the better sphygmomanometer, universally available
(4) in blood chemistry abnormalities	
By few and crude methods	By many easily available methods, but with no greatly significant results
II. Symptomatic	
A. In the presence of indications of toxemia	
(1) Rest in bed	
(2) Fresh air	
(3) Dietetic	
Restriction of dietary proteins best exemplified in exclusive milk diet	Restriction of salt, compensation for protein loss, rarely by water restriction
(4) Stimulation of gastrointestinal elimination by salines	
By a great variety of active mineral and vegetable purgatives	By enemas—occasionally by castor oil and high colonic irrigations. Lavage
(5) Stimulation of kidneys by copious liquid intake; by digitalis	
By saline diuretics; by dry or wet cups; by leeches	By intravenous administration of hypertonic glucose; occasionally hot fomentations; high colonic irrigations; occasionally synthetic diuretics
(6) Reduction of hypertension by venesection	
Esteemed of utmost importance	Rarely used. Believed generally transitory only in effect
(7) Induction of labor	
B. Convulsions having actually supervened	
(1) Isolation, quiet, good nursing, protection from injury	
(2) Purging	
Elaterium or croton oil, or calomel or jalap	Not so universally used, but still stressed by some, especially the Dublin School
(3) Venesection	
Most important measure	Used occasionally by most authorities
(4) Control of convulsions	
By chloroform—augmented by morphine and chloral; *Veratrum viride*	By morphine—augmented by chloral and chloroform by Stroganoff; chloroform condemned by most Americans. By magnesium sulfate intravenously. By various synthetic drugs, especially the barbiturates. Veratrone
(5) Termination of pregnancy	
Up to recent years regarded as paramount by most authorities, but even in early days some advocated conservatism. In the early years of this century accouchement forcé much used and much abused. Barker said (1883): "Whenever delivery by art can be effected by less irritation than would be produced by the continuance of the child in the parturient canal, it should be resorted to." This statement, I believe, is still eminently valid.	The pendulum of opinion in recent years is strongly conservative. The greatest teachers of our day almost accuse one with the temerity to advocate radicalism of murder. Their statistics are frequently unfair, however, in contrasting brutal accouchement forcé without selection of cases, with their conservative treatment, rather than making the comparison with modern operative techniques and innocuous methods of anesthesia. They give little consideration to fetal survival

Method of Treatment

Prophylactic treatment includes the entire regime of antenatal care. This connotes frequent close observation of all pregnant women from the earliest time possible. History, blood pressure, urinalysis, weight, general signs and symptoms should all be noted and carefully analyzed from time to time.

If abnormalities indicative of toxemia develop, the regime must be intensified by rest, varying from minimal restriction of activity to hospitalization and complete bed rest. The last is the *most important single item* of prophylaxis and of the treatment of the milder cases. Diet must be restricted as to carbohydrates and total calories sufficiently to control excessive weight gain. In the presence of marked rapid weight gain, which usually indicates occult edema, or in any evidence of actual edema, salt should be restricted.

Simple urinalysis is supplemented by estimations of the renal capacity, of blood chemistry, and sometimes of hepatic function. The liquid intake and urinary output should be closely watched and correlated. Bowel function is maintained by mild catharsis, usually with salines, enemas, and, much less frequently than formerly, by high colonic irrigations. Only mild and minimal sedation is employed in cases of this mild type.

Failure of the mild type to improve under such a regime, or its progression to constantly more menacing symptomatology, should in a reasonably short time lead to the consideration of the termination of pregnancy. The means adopted will depend on age, parity, previous pregnancy and labor history, duration of pregnancy, viability of child, social, religious, and personal considerations peculiar to the indiviudal patient, the severity of the condition, the presence of special symptoms, and the estimated imminence of disaster.

Means employed for this purpose are usually medicinal, comprising castor oil, enemas, and the exhibition of fractional doses of pitocin, sometimes augmented by artificial stripping and rupture of the membranes. Other mechanical means, such as bagging or the use of bougies, are rarely resorted to. It is generally preferable to make, if necessary, several attempts at such medical induction, rather than to risk not always promptly successful mechanical procedures with their high potentiality of infective complication. In the presence of fulminant progress of the case toward explosive eventuality, cesarean section for delivery should be unhesitatingly resorted to.

In this connection, the anesthesia is of great importance. No inhalation anesthetic should be used, but lower neuron anesthesia by local infiltration, intrathecal or caudal instillation, should be employed.

In those types of late pregnancy toxemia depending on pre-existing disease, as the nephritides, and the various forms of fixed hypertension, the same general regime is applicable except that the medical management must be more rigorously instituted and maintained and more prompt resort to termination of the pregnancy must be carried out. The importance of this time factor will be discussed in greater detail presently.

If the patient develops or is first seen in an actual state of eclampsia, the following outline of treatment is carried out:

1. Segregation of the patient, darkening of the room, elimination of all possible causes of disturbance from the environment, provision of competent, constant nursing care.

2. Provision of facilities to guard the patient against injury during convulsions.

3. The administration of 20 c.c. of a 10 per cent solution of magnesium sulfate intravenously at one-hour intervals as long as convulsions persist. As their frequency subsides, the dosage is progressively cut down to four-, eight-, and twelve-hour intervals. It is continued at the last rate for at least twenty-four hours after convulsions have stopped.

4. An initial dose of morphine sulfate ¼ grain by hypodermic may be given. It is usually not repeated because of its repiratory depression.

5. Other sedatives such as bromides, chloral, various barbiturates may be used. If they are, they should be used in substitution for, rather than in addition to, morphine and magnesium sulfate. Every sedative available in eclampsia is itself a poison. To multiply the number of such agents simultaneously given to one patient is to risk the incalculable synergistic effect of several poisons on a woman already manifestly severely poisoned. Determine what sedative you will rely on, then stick to it!

6. Three hundred cubic centimeters of 25 per cent dextrose solution are given intravenously and repeated at intervals of from four to twelve hours. This acts to reduce edema and as a direct diuretic. The rate of administration of this solution should not exceed 4 c.c. per minute.

7. Draining of tracheal mucus by inverted posture of the patient and by direct aspiration is practiced when necessary.

8. Venesection is used only in right heart failure.

9. Liquids of high carbohydrates equivalent are given as soon as the patient has recovered consciousness and can swallow.

10. It will be noted that this scheme of management does not contemplate any effort to terminate the pregnancy, during the actual period of convulsion and/or coma. Labor may occur spontaneously during this phase of the patient's condition and progress to successful termination. Even when this occurs, however, no artificial interference is employed, except occasionally very simple low forceps extraction to expedite the delivery. We have not for many years resorted to cesarean section in the presence of actual eclampsia, inasmuch as we believe, on the basis of long-time experience, that this increases the hazard to the mother and that the prospect of fetal salvage is very, very small.

However, if the patient recovers from the eclamptic crisis undelivered and with a viable baby, we believe that within a period of a very few days the pregnancy should be terminated as already described under prophylaxis. We feel that she has reverted to a status of severe pre-eclampsia and may be in very definite danger of recurrence of eclamptic seizure.

Results

The Margaret Hague Maternity Hospital has now been in operation a little over thirteen years, during which time there have been born approximately 70,000 living babies. This material has embraced many hundreds of toxemia patients. For several years Dr. Leon C. Chesley, our biochemist, has been very much interested in all phases of this subject. Together with a number of coworkers, notably his wife, Betty Chesley, and Drs. Willard Somers and John McGeary of our staff, both now in the Army service, he has been especially interested in follow-up of this group. From these follow-up studies certain valuable points of emphasis in relation to the management already outlined may be deduced.

The primary objective of all management is (*1*) to reduce maternal mortality. The most direct secondary objectives contributing to this primary purpose are (*2*) the prevention of eclamptic convulsions, and (*3*) the prevention of abruption of the placenta. Next to the life hazard of the mother, (*4*) the life hazard to the fetus in abortion, stillbirth, and neonatal death becomes the most important consideration of management. Finally (*5*) the reduction of remote hazard of death to the mother by the prevention of permanent sequelae, notably fixed hypertensive states, is a further objective.

A summary of 1,625 cases of toxemia occurring in a five-year period, 1935 through 1939, shows:

A maternal mortality of 1 per cent.
An incidence of abruption of the placenta of 3.8 per cent.
An incidence of eclampsia of 5.5 per cent.
An incidence of total fetal loss of 17.1 per cent.
An incidence of remote permanent hypertension of 53 per cent.

The whole question of treatment, therefore, depends on how much we can reduce these several hazards, the protection against which are the objectives of treatment.

In this connection it must be immediately recognized that prophylaxis cannot, except possibly in a very small degree, prevent the actual occurrence of toxemia. The most that prophylaxis can accomplish is recognition of the very first danger signals of toxemia in order that further management may avert in some measure the hazards under consideration.

Our statistics would appear to show that the prompt control of even the mildest cases of toxemia is essential in cutting down those hazards, because they increase definitely with the progress of the disease from milder to more severe forms. Thus, we had only one death in 1,232 cases of mild pre-eclampsia, renal disease, and unclassified toxemia, but there was one death in every twenty-four cases of severe pre-eclampsia, eclampsia, and hypertensive disease. The appearance of convulsions increased the maternal mortality rate almost ten times.

But it is further noteworthy that not all cases exhibit systematic progression in severity. One cannot assume that a case of *mild* pre-eclampsia is in no danger of eclampsia because she has not progressed to a *severe* grade of pre-eclampsia before the onset of convulsions. Almost two-thirds of all our eclampsia occurred in cases which we had considered mild pre-eclampsia. Or, to state the equation the other way around, one out of every 29 of our mild pre-eclampsias became abruptly eclamptic without exhibiting any intermediate phase which would warrant their consideration as severe pre-eclamptics.

Much the same consideration holds for the incidence of abruption of the placenta. While it is true that the incidence of this condition did increase with the severity of the toxemia, it still occurred in mild pre-eclamptics in a ratio of 1 in 50 cases.

Thus, from the standpoint of the mother, in order to protect her from the possibility of abruption, of eclampsia, of a high mortality rate, and the later occurrence of fixed hypertension, the prompt control of an existing toxemia of any grade whatever would appear to be paramount. The only effective means accomplishing this control is termination of the pregnancy. Therefore, the crucial consideration is the time interval between the first exhibition of any degree of toxemia whatever, and the termination of the pregnancy.

How does such prompt termination affect the interest of the baby? This, of course, would depend somewhat on the period of gestation. Before thirty-four weeks the baby is more or less surely jeopardized by prematurity. Hence there would appear superficially to be an a priori conflict of interest between the mother and the baby. This conflict is more apparent than real, however. While it is true that the baby, prior to this period of gestation, is more seriously jeopardized by prematurity, the continuance of its intrauterine existence by no means insures a better life prognosis. Many of these infants die in utero, apparently of the direct effects of the mother's illness on the fetus. Should the mother develop either abruption or eclampsia, these conditions per se represent a tremendous hazard to fetal survival. If these three fetal hazards be offset against the single fetal hazard of prematurity, it is apparent that the fetus is not much more significantly jeopardized by the termination of the pregnancy at any time from the period of viability up to the thirty-fourth week than it would be if the pregnancy were carried further in the assumed interest of the fetus.

After the thirty-fourth week, the termination of the pregnancy in the mother's interest would appear to act just as significantly in the fetal interest, because the baby from this time on is subjected to much less of a hazard by reason of prematurity, while the longer the pregnancy continues, the greater becomes the hazard to the fetus of the other three factors discussed above.

Thus it can very definitely be stated that prompt termination of the pregnancy in the presence of established toxemia after the thirty-fourth week of gestation serves alike and directly both the maternal and the fetal interest.

It also serves to prevent fixed hypertension as a sequela of the toxemia. This clinical condition, or rather symptom, is selected as a gauge typifying all the sequelae of pregnancy toxemia because of its ease of estimation and the relative frequency with which it occurs as compared with other possible sequelae. Also, it is important as indicative of the progressive vascular-renal disease probably constituting the aftermath of such toxemias.

Survey of the actual medicinal components of the management of toxemias in our clinic shows a wide variety of specific agents and combinations of such agents, from which no sure conclusion can be drawn as to the outstanding comparative value of any. It is probable that this statement might be extended to apply just as validly to all the many agents, combinations of agents, and so-called methods or systems, which have been everywhere employed.

What have been the results of the vast amount of work which has been performed in the attempt to reduce toxemic mortality in pregnant woman? In a broad statistical sense there has been a real and fairly regularly progressive reduction in such mortality. But it is noteworthy that this decrease in maternal hazard from toxemia has been closely parallel to the general decrease in maternal mortality from all causes. This is to some extent natural and understandable. The improvements in general prenatal observation, in surgical technique, in nursing technique, in knowledge and resources having to do with the replacement of lost blood volume, and in chemotherapy, which have contributed so tellingly to the reduction of hazard in the other great causes of maternal mortality, namely, hemorrhage and infection, have all benefited equally the toxemic patient. Beyond the influence of such factors common to all the causes of maternal death, we believe that the improvement already obtained in deaths from toxemia, and the promise of greater improvement depend upon:

1. The general employment of close prenatal supervision of all pregnant women.
2. Recognition of the actual appearance of toxemia at the earliest possible time.
3. Increasing hospitalization of pregnant women.
4. Prompt institution of bed rest and suitable medical treatment of even mildest cases.
5. The early interruption of pregnancy in all cases, except those of the mildest type whose symptoms entirely clear up under rest and medical regime. This is especially important beyond the thirty-fourth week of gestation.
6. The elimination of meddlesome midwifery of all sorts from the management of the convulsive toxemias.

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ORAL THERAPY WITH ETHINYL ESTRADIOL IN THE MENOPAUSE

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THE value of estrogenic preparations in the treatment of the menopausal syndrome is firmly established. Ever since chemically pure estrogens became available, the medical profession has sought earnestly for compounds which, when given orally, have the distinction of high potency, good tolerability, and economy. In 1938, Inhoffen and Hohlweg[3] prepared a derivative of estradiol by replacing the hydrogen atom at carbon atom 17 with an ethinyl group. It is claimed that the new compound fulfills the requirements of great effectiveness when administered by mouth, of comparative absence of unpleasant side reactions, and of inexpensiveness. Clinical results with ethinyl estradiol in climacteric patients have been described only by a limited number of investigators; hence a report of further experiences along these lines seems warranted.

Material and Procedure

The series under investigation consisted of 53 patients, ranging in age from 34 to 51 years, who were suffering from climacteric symptoms. There were 27 cases of natural menopause, 21 cases of surgical menopause, and 5 cases of radiologic menopause. In 15 patients, bleeding which still persisted ranged from oligomenorrhea to hyperpolymenorrhea. Almost all patients complained of hot flushes, diaphoresis, tingling in extremities, and other symptoms which may be classified as vasomotor nervous or general. As for basal metabolic dysfunction, two-thirds of the patients stated that there was a weight increase of fifteen pounds or more during the last few years. A history was taken in every case and the patient thoroughly examined—this included a careful pelvic examination. In all those exhibiting excessive bleeding, the presence of intrauterine pathologic processes was ruled out by means of a diagnostic curettage.

The cytology of the vaginal epithelium was studied in all cases. Smears were taken before treatment, and several times during and after. The single differential stain was used according to the simplified technique of Shorr.[6]*

In addition, pre- and postmedication biopsy studies were performed in ten cases in order to determine the effect of ethinyl estradiol on the endometrium.

Finally, in seven of these patients and in three others of the series, assays of urinary prolans and estrogens were performed prior to initiation of therapy.

The prolans were assayed in a morning specimen and the estrogens in a twenty-four-hour specimen. The prolans were extracted by utilizing the modification of Zondek's method. A fresh refrigerated specimen of urine was slightly acidified with dilute acetic acid. Ethyl alcohol was added and the mixture allowed to stand from two to twenty-four hours, then centrifuged and the supernatant fluid discarded. Ethyl ether was added, well shaken in order to break up the precipitate, which removes the estrogenic substances, again centrifuged and the supernatant fluid discarded. The precipitate was dried until all ether had evaporated. Distilled water was added and constantly shaken for ten minutes, again centrifuged and the

*The Kit devised by Dr. Brent of Roche-Organon, Inc., which contains all the material necessary for the preparation of vaginal spreads, proved most practical for this purpose.

supernatant fluid, which contains the gonadotrophic hormone, saved. Three immature female mice weighing from 6 to 8 grams were injected twice daily for three days. The mice were not injected on the fourth day and were autopsied on the fifth day or one hundred hours after the first injection.

The estrogens were extracted by using the Kurzrok and Ratner method. Nine hundred cubic centimeters of the twenty-four-hour urine specimen were made slightly acid with dilute acetic acid, then saturated with sodium chloride. The treated urine was then covered with ethyl acetate to the top of the flask. A second flask was filled with 200 c.c. of ethyl acetate and attached to the first flask. The hot plate was turned on to medium heat and the ethyl acetate distilled over, and condensed. It dropped to the bottom of the first flask from which it returned to the second flask. The drops of ethyl acetate in passing upward through the urine extracted the hormone. This provided continuous extraction for forty-eight hours. The extracted urine was then discarded and the ethyl acetate extract, which contains the hormone, was concentrated by vacuum distillation. To the remaining substance 6 c.c. of propylene glycol were added. This solution was then injected into ovariectomized rats. The animal assay consists of injecting a definite dosage of the solution in three equal doses, and twenty-four hours later making a vaginal smear. A positive smear must show the cornified cells characteristic of estrus.

No hormone estimations were carried out following termination of therapy, partly because of the expense involved, and partly because the patients, no matter how cooperative they were while symptoms were severe, did not want to "bother" with collecting the urine specimens once they had found relief.

At the initiation of the investigation, one tablet containing 0.05 mg. of ethinyl estradiol* was given three times a day. If side effects occurred, the medication was stopped for four days and the dosage then reduced to 0.05 mg. a day, and this was increased later as needed. This plan was found unsatisfactory and was abandoned. Instead each patient was started on 0.05 mg. a day, given in two divided doses, and this whenever indicated was increased after a few days to a daily total of 0.1 mg. and sometimes to a daily total of 0.15 mg. In general, before shifting to maintenance dosage, the maximum therapeutic dose employed in a given patient was kept up for three to four weeks. Then the daily dose was reduced; in many cases as little as 0.025 mg. (half a tablet) maintained the patient in comfort.

Clinical Results and Laboratory Findings

Satisfactory relief of symptoms followed administration of ethinyl estradiol in all cases within six to nine days. Forty-three women showed complete relief and ten were markedly benefited. Patients who were started on the original dosage plan (0.05 mg. three times daily) in general experienced relief sooner than those who were started on a daily dose of 0.05 mg. and whose hormonal intake was then built up gradually.

Significant side reactions occurred only in patients who from the beginning were given a total daily dose of 0.15 mg. Of these, 6 patients developed gastric distress after two or three days of medication. These undesirable by-effects subsided, however, on discontinuation of the drug and were not provoked again in any case on reduced dosage. In twelve patients, each of whom had received a total dosage of 3.15 mg., given over twenty-one days, withdrawal bleeding occurred when the dosage was reduced. Moreover, in eight cases there was withdrawal bleeding after cessation of medication. As for the total requirements, those patients who still continued to menstruate, although climacteric symptoms had begun, needed the smallest total dosage. In those women who had undergone natural menopause, a somewhat larger total dosage was necessary, and in cases of artificial menopause, the needs were still a little higher. However, in all of these groups the requirements were minute as compared with other oral estrogens.

Preliminary vaginal smears in the majority of instances revealed marked estrogen deficiency characterized by "atrophy" cells and an abundance of leucocytes. Smears studied

*The ethinyl estradiol tablets, (Lynoral) 0.05 mg., used in this study were supplied through the courtesy of Dr. Leo A. Pirk of Roche-Organon, Inc., Nutley, New Jersey.

when patients were changed to the maintenance dose usually showed good cornification. However, not in all cases did the smear picture parallel the subjective response experienced by the patient.

The premedication biopsy studies revealed an atrophic endometrium in five instances and some degree of proliferation in five others. Specimens, taken between fourteen and twenty days after initiation of therapy, showed a cystic and glandular hyperplasia of the endometrium in one instance, and good proliferation in all others.

Preliminary urinary prolans were present and estrogenic hormones absent in the cases investigated.

Case Reports

Four cases are reviewed briefly partly because their histories illustrate the procedure employed and the results obtained, partly because of the interesting features encountered.

CASE 1.—B. H., aged 50 years, para iii, gravida iii. Menarche occurred at 13 years of age with cycles of 28 days and a menstrual flow lasting three to four days. A year ago menstruation ceased abruptly. Patient complained of 24 to 28 flushes a day. Pelvic examination revealed: a normal vagina; a clean, multiparous cervix; a small, atrophic, movable uterus; and normal uterosacral ligaments and adnexae. The vaginal smear showed atrophy cells and leucocytes. A biopsy specimen revealed an atrophic endometrium. Urinary prolans were present and estrogenic hormones absent. Five-hundredths of a milligram of ethinyl estradiol were administered three times a day. After eight days there were only two to three flushes a day. The vaginal smear on the fourteenth day of therapy showed some atrophy cells and numerous well-cornified epithelial cells. An endometrial biopsy study carried out on the same day revealed good proliferation. The daily dosage of 0.15 mg. of ethinyl estradiol was well tolerated and maintained for three weeeks. During this period there were only occasional hot flushes at night and consequently the dosage was shifted to 0.05 mg. a day. On this maintenance dose, which was kept up for three months, the patient did very well.

CASE 2.—H. W., aged 34 years, para i, gravida i. Menarche occurred at 15 years of age with cycles of 32 days and a menstrual flow lasting four to five days. In July, 1944, a panhysterectomy and bilateral oophorectomy had been performed. Three months postoperatively, patient experienced severe vasomotor symptoms which constituted her main complaint at the first consultation. The vaginal smear showed atrophy cells and leucocytes. In the urine, prolans were present and estrogenic hormones absent. Five-hundredths of a milligram of ethinyl estradiol were given three times a day. On the third day the patient developed gastrointestinal symptoms (nausea and vomiting) and consequently the medication was discontinued for four days. Thereafter on reduced dosage—0.05 mg. a day for three days—there was no recurrence of side reactions. Increase of dosage to 0.05 mg. twice a day was also tolerated well. This was kept up for eleven more days. At that time there were mild symptoms only, and a vaginal smear study on the seventeenth day of medication showed atrophy cells and small epithelial cells with large nuclei. Then the dosage was shifted to 0.05 mg. a day. On this maintenance dose, which was kept up for three months, the patient did very well.

CASE 3.—L. S., aged 48 years, para iv, gravida iv. The menstrual history was a normal one until three months prior to her presentation. At that time a severe menorrhagia required roentgen-ray castration. Patient complained of frequent hot flushes, marked vertigo, and nervousness. Pelvic examination revealed: a slight cystocele and rectocele; a clean, multiparous cervix; an antiflexed, movable uterus of normal size; and normal uterosacral ligaments and adnexae. The vaginal smear showed atrophy cells and small epithelial cells with large nuclei. A biopsy specimen revealed a proliferative endometrium. (Fig. 1*A*.) Urinary prolans were present and estrogenic hormones absent. Five-hundredths of a milligram of ethinyl estradiol three times a day was tolerated well and was followed by marked improvement.

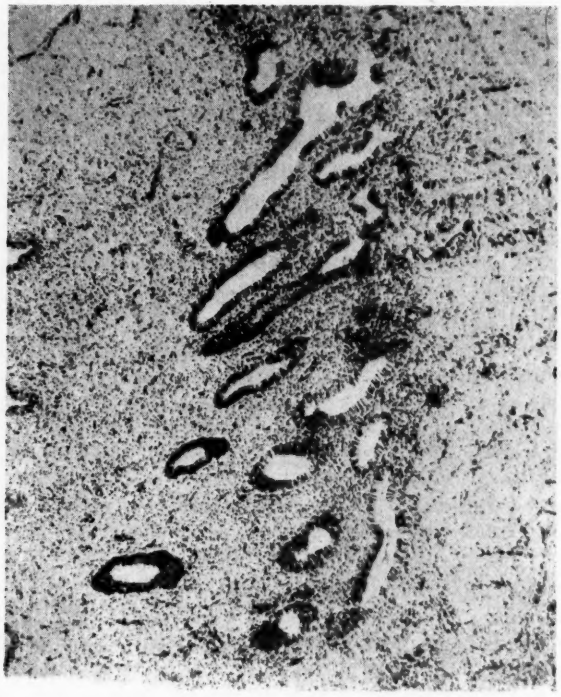

Fig. 1A.—Case L. S., aged 48 years, radiologic menopause; preliminary endometrial biopsy showing a proliferative phase.

Fig. 1B.—Same case, after seventeen days of treatment with the higher dose of 0.15 mg. ethinyl estrodiol a day, showing cystic and glandular hyperplasia.

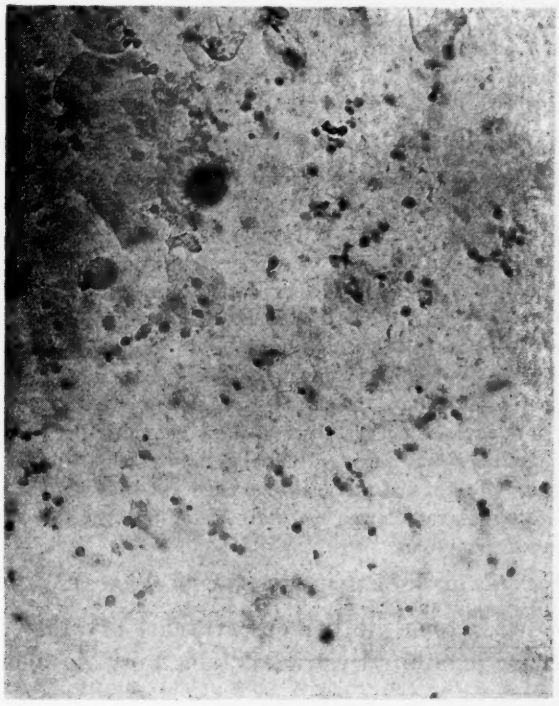

Fig. 2*A*.—Case M. W., aged 50 years, natural menopause; preliminary vaginal smear showing marked estrogen deficiency.

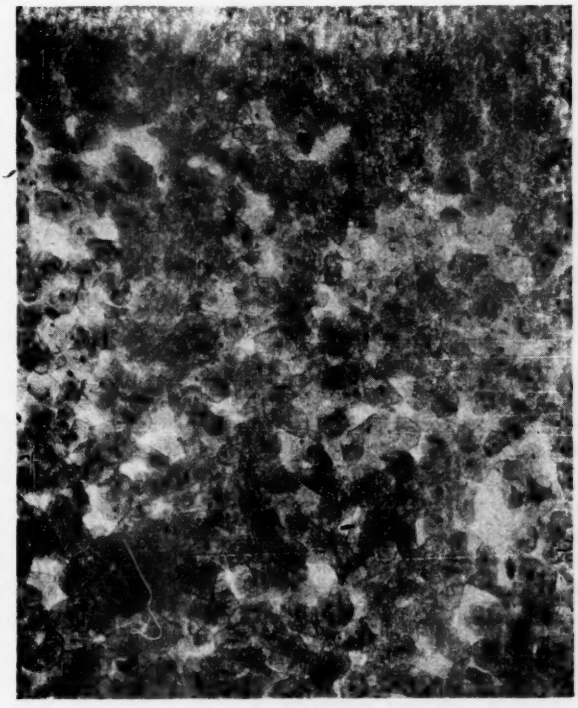

Fig. 2*B*.—Same case, after eighteen days of treatment with ethinyl estradiol, showing clean appearance and large epithelial cells with small pyknotic nuclei.

There were only one to two flushes after seven days of treatment. A vaginal smear, made after seventeen days under this regimen, showed complete cornification. An endometrial biopsy study carried out on the same day revealed cystic and glandular hyperplasia (Fig. 1*B*). Then the dosage of ethinyl estradiol was reduced to 0.05 mg. daily. On this maintenance dose, which was kept up for three months, patient was completely free of symptoms.

CASE 8.—M. W., aged 50 years, para ii, gravida ii. Menarche at 16 years of age with cycles of 28 to 30 days and a menstrual flow lasting three to four days. Menses had ceased one and one-half years ago. Patient had 20 to 30 flushes a day and with spells of vertigo for which she sought medical attention. Pelvic examination revealed: a normal vagina; a multiparous cervix with a slight erosion on upper lip; an anteflexed, movable uterus of normal size; and normal uterosacral ligaments and adnexae. The vaginal smear showed marked estrogen deficiency (Fig. 2*A*). A biopsy specimen revealed a proliferative endometrium. Urinary prolans were present and estrogenic hormones absent. Satisfactory clinical relief of symptoms was noted after one week, on a daily dosage of 0.1 mg. of ethinyl estradiol given in two divided doses. Thereafter patient was satisfactorily maintained on a daily dose of 0.05 mg. A vaginal smear taken on the eighteenth day of treatment was characterized by its clean appearance and large epithelial cells with small pyknotic nuclei (Fig. 2*B*). An endometrial biopsy study carried out at this time revealed late proliferation. A daily dose of 0.05 mg. of ethinyl estradiol was maintained for another three months and this kept patient completely free of symptoms.

Discussion

Table I summarizes some of the observations of other investigators who have discussed the use of ethinyl estradiol tablets in the menopause.

TABLE I. ETHINYL ESTRADIOL TABLETS IN THE MANAGEMENT OF THE MENOPAUSE AS REPORTED IN THE LITERATURE

REPORT	NO. OF CASES	FAILURE OF RESPONSE	DAILY DOSAGE FOR MOST PATIENTS
U. J. Salmon, S. H. Geist, R. I. Walter, and N. Mintz[5]	22	2	0.45 mg.
B. A. Watson[8]	18	1	0.45 mg., 3 days 0.30 mg., 2 days 0.15 mg., daily
M. J. Groper and G. R. Biskind[1]	33	4	0.05-0.45 mg.
S. D. Soule[7]	30	2	0.05 mg.
R. A. Lyon[4]	45	0	0.05 mg.
F. E. Harding[2]	32	0	0.05-0.1 mg.

The series studied by the various workers consisted of from 18 to 45 patients. Relief was obtained in these groups in from 87.8 per cent to 100 per cent. This includes excellent as well as partial relief of symptoms. The daily therapeutic dosage ranged from 0.05 mg. to 0.45 mg. The incidence of toxic manifestations varied greatly in the hands of these investigators. Salmon et al.[5] observed nausea, vomiting, abdominal pain and malaise, necessitating cessation of therapy, in four out of 22 patients. These side reactions were induced with 0.3 mg. of ethinyl estradiol as the daily dose. Three other patients had similar gastrointestinal symptoms which, however, subsided on reduced dosage. Of the 18 cases studied by Watson,[8] only one patient experienced such severe side effects—nausea and urticaria—that the medication had to be discontinued. Even as little as 0.05 mg. a day elicited these symptoms. Another woman complained of slight nausea and soreness of the breasts and vagina. Groper and Biskind[1] in their series of 33 patients observed three instances of severe headache but in only one did it become necessary to discontinue the drug. Soule,[7] who treated 30 women, found a daily dosage of 0.05 mg. to be therapeutically satisfactory. Under this plan he observed two instances of gastrointestinal symptoms requiring cessation of medication. Lyon,[4] studying 45 patients, likewise employed a daily dosage of 0.05 mg. This induced slight nausea in five cases.

Finally, Harding[2] observed four instances of "true toxic reactions" (nausea, vomiting, dizziness) in his group of 32 climacteric women. These side effects were experienced on a daily dosage of 0.1 or 0.2 mg.; with smaller dosage in three of these cases toxic symptoms subsided. No attempt was made to reduce the dosage of the fourth patient.

In the present study undesirable by-effects—gastrointestinal distress—were observed only on a total daily dosage of 0.15 mg. in six cases. Symptoms disappeared promptly when the dosage was reduced to its minimal effective level. This was 0.05 mg. a day and there was no recurrence of symptoms in those patients whose daily dosage plan was later increased. But it is felt that in general and if symptoms are not too severe, satisfactory response is obtained with a daily dose of 0.05 mg. This is in keeping with the findings of other investigators, particularly those of Soule[7] and Lyon.[4] The fact that such a small dose of ethinyl estradiol is effective shows its high potency when given by mouth as compared with other estrogens which lose about 90 per cent of their activity when passing through the gastrointestinal tract.

Summary and Conclusions

A series of 53 women with menopausal symptoms was treated with ethinyl estradiol. All were satisfactorily relieved six to nine days after institution of therapy. The initial treatment plan, which called for 0.05 mg. of ethinyl estradiol three times daily, was abandoned since side effects occurred in 6 patients. By reducing the daily dose to 0.05 mg., gastrointestinal disturbance could be eliminated completely. Consequently, the initial daily dose in all patients was changed to 0.05 mg. This dose was tolerated well without exception and could be increased with impunity. The optimal therapeutic amount was given for three to four weeks after which the daily dose was reduced to a maintenance level.

Repeated vaginal smear studies were carried out in all cases. Endometrial specimens of ten patients were studied before institution of therapy and after ethinyl estradiol had been administered for two to three weeks. Premedication hormone assays were performed in ten cases.

Clinical results of other investigators with ethinyl estradiol in climacteric patients are discussed.

The new estrogen is very effective when administered by mouth. There is complete absence of side reactions if minimal effective doses are administered.

We wish to thank Dr. H. C. Taylor, Jr., for his constant advice and encouragement.

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PYRIDOXINE FAILURE IN NAUSEA AND VOMITING OF PREGNANCY

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HYPEREMESIS gravidarum occurs very infrequently. The less serious nausea and vomiting is far more common, but its incidence is difficult to evaluate because the patients may not report it, or they may not report for prenatal care until they have more or less passed the period of this distress. Nausea alone is thought to be frequent, and it is still more difficult to evaluate inasmuch as there is no physical or external means of proving its intensity, duration, and frequency. Dieckmann's[7] definitions and classification are employed throughout. The purpose of this report is to present observations on the value of B_6 or pyridoxine as a therapeutic agent for nausea and vomiting of pregnancy.

Numerous chemical agents and procedures have been tried and used with varying degrees of success. Frequently a proponent will follow a given procedure for a given time and then finally discontinue its use without retracting his previously published recommendations. Thus, the literature remains flooded with endorsements which in many instances should have long since been retracted. Vitamins and vitamin therapy have been given credit for many values as therapeutic agents. There is no question about the place and need of certain vitamins in certain conditions.

Hart, Sydenstricker, and Torpin,[1] in 1941, used a pill which contained thiamine, riboflavin, nicotinamide, pyridoxine, and calcium pantothenate in the treatment of nausea and vomiting of pregnancy. They report that usually there was cessation of vomiting and partial relief of nausea within two to three days after treatment had been instituted. Furthermore, it was their conviction that, if this preparation had been instituted early in pregnancy and continued with one tablet after each meal, the patient would remain free from this annoyance of pregnancy. Recurrence would take place in one or two weeks, in some instances, after they discontinued the tablet. It should be stated that their series consisted of sixteen mild cases.

In 1942, Willis, Winn, Morris, Newsom, and Massey[2] used thiamine chloride and pyridoxine. Of 46 patients on thiamine chloride, good results occurred in 30; fair, in 10; and poor, in 6. Whereas, of the 37 patients on pyridoxine, good results were found in 25; fair, in 8; and poor, in 4. All their treatments were given intramuscularly and intravenously. In their article they state that "almost complete relief from nausea and vomiting of pregnancy was gained by administering vitamin B_1 and B_6 in varying dosage at irregular intervals and by either the intramuscular or intravenous routes." In spite of the fact that the percentages of good results are about comparable for thiamine and pyridoxine, they add that relief occurred from nausea and vomiting more often from the use of B_6 than B_1.

Weinstein, Mitchell, and Sustendal,[3] and Weinstein, Wohl, Mitchell, and Sustendal[4] have offered the following observations. The former group stated, "While the use of pyridoxine hydrochloride has proved of value in these 32 patients, the importance of sedation and adequate dietary supervision should not be overlooked, but should be prescribed as usual with pyridoxine hydrochloride used as an integral and valuable portion of this regimen." A few

months later, the latter group had increased their series from 32 to 78 patients. Relief was noted in 68 by the use of 30 to 80 mg. pyridoxine orally for the less severe patients and 100 mg. daily for the severe ones. Again they find that "the use of pyridoxine hydrochloride has proved of value in this group of 78 patients. However, the value of sedation and adequate dietary supervision should continue to command our attention, and should be utilized with pyridoxine hydrochloride as an important adjunct in the therapy of nausea and vomiting of pregnancy. A far larger series of patients must be carefully analyzed before final conclusions can be reached."

By contrast, Smith,[5] making a report, did not give the data on the number of patients treated. He did recommend a complete history and physical examination, careful investigation for pyelitis, cystitis, abscessed teeth, and vaginal and cervical infection. He gave liver extract intramuscularly and 100 mg. thiamine chloride and 50 mg. pyridoxine hydrochloride intravenously daily for three days and then weekly as needed. The patients returned for further treatment only when the first signs of nausea reappeared.

Silbernagel and Burt[6] had complete relief in 38 out of 40 patients by the use of intravenous pyridoxine hydrochloride. Their dosage varied from 25 to 50 mg. Twenty-two of this number had been on intravenous therapy with complete and permanent correction. Repeated injections were given only when symptoms recurred. They took special care not to alter the diet or to prescribe sedatives.

It is impressive that the above authors could collect in short periods the number of patients with sufficient symptoms to require treatment. At the Chicago Lying-in Hospital there are very few admissions with vomiting of pregnancy, and not all of these are classed as hyperemesis gravidarum. Only 2 of the 16 patients of our series required hospitalization and but 1 was a hyperemesis gravidarum case. Hence, the other 14 patients had only minimal or moderate nausea and vomiting. It is our contention that patients with hyperemesis gravidarum should be hospitalized to obtain proper treatment. The treatments for this series were given in two orders. The first group was placed on pyridoxine, 100 mg. daily by mouth and 100 mg. pyridoxine intramuscularly twice weekly. Out of the 11 patients that had pyridoxine initially, only 3 had good results, 3 had fair results, and 5 had poor results. Placebo therapy was used in 3, secondarily. One of these obtained good results on placebo therapy subsequently and another one had an excellent result with moderate sedation.

The control group consisted of 5 patients who were initially placed on placebo therapy. The tablets were the same size as the pyridoxine one and given in the same manner and number. Thus, when a change was made, the patient was not aware of it. Three of these 5 patients were completely relieved of their nausea and vomiting by sterile water intramuscularly injected and placebo tablets. Two had poor results and were later placed on pyridoxine. The one patient with hyperemesis gravidarum in the entire series was benefited only when electrolytes, body fluids, and other deficiencies were corrected in accordance with Dieckmann's[7] routine.

Tables I and II give additional data about these patients, including age, the number of previous pregnancies and complications, and the weeks of gestation when treatment was instituted.

TABLE I. EFFECT OF PYRIDOXINE (B_6) UPON HYPEREMESIS, AND NEED FOR OTHER THERAPIES

CASE	AGE (YR.)	GRAV.	PARA	COMPLICATIONS		WEEKS PREG.	SUBSEQUENT THERAPY		REMARKS	RESULTS OF B_6
				PRIOR PREG.	PRESENT		PLACEBO	OTHER		
1	22	i	o		Fear	12			Phenobarbital for sleep	Good
2	26	ii	i	Stillbirth		10				Good
3	28	iii	ii	Stillbirth		8			"Doesn't need shots"	Good
4	22	ii	i	Endometritis		10		X		Fair
5	29	ii	i			8	X			Fair
6	30	ii	i	Breast abscess		9		X		Fair
7	26	i	0		Obsession	8		X		Poor
8	31	i	0			14	X (good result)			Poor
9	37	iii	ii			10		X (good result)		Poor
10	38	ii	i	Long labor; Dührssen incision		8		X		Poor
11	38	iii	ii		Twins	8	X	X		Poor

TABLE II. EFFECT OF PLACEBO THERAPY UPON HYPEREMESIS, AND NEED FOR OTHER THERAPY

CASE	AGE (YR.)	GRAV.	PARA	COMPLICATIONS		PREG. WEEKS	SUBSEQUENT THERAPY		REMARKS	RESULTS OF PLACEBO
				PRIOR PREG.	PRESENT		B_6	OTHER		
12	23	ii	i			9				Good
13	27	ii	i	Abortion		8			Hospitalized	Good
14	35	iii	ii			6				Good
15	31	iv	ii	1 abortion 3 hyperemesis		7	X	X (good result)	Hospitalized	Poor
16	33	iii	0	Ectopic and abortion		8	X		"Hypos" helped most	Poor

Particular efforts were made to have the patients make no change in dietary and other habits and routines. All of those who failed to respond to either the pyridoxine or "placebo" therapy were cured by appropriate sedation and dietary management.

The less severe cases were treated for two or more weeks before changing the treatment if a good result had not occurred. The more severe cases and those hospitalized required relief in shorter time. Those in the hospital had 100 mg. pyridoxine hypodermically daily. This assured that the vitmain was not lost by vomiting or was not assimilated due to deranged gastrointestinal state. Possibly two weeks was too short a minimum time, but those carried longer appeared not to do any better.

When good results, or arrest of vomiting and relief of nausea took place, it did so usually within a few days in both the pyridoxine as well as the control group.

There has been no evidence that those patients who required sedation, dietary, and other therapies for cures improved any more rapidly after the pyridoxine administration than those who did not receive it. It is possible that the dosage was inadequate but by comparison with the previous reports a sufficient amount was given.

It must not be forgotten that most patients became relieved of their nausea and vomiting about the end of the first trimester of pregnancy. Hence, any improvement may be spontaneous or natural. Certainly some patients are benefited by assurance. A fairly large number of these patients had had complications in previous pregnancies or attitudes during this one which might well be associated with an emotional imbalance. It is admitted that neurotic or psychoneurotic states might be major factors in the nausea and vomiting of pregnancy, but it is our conviction that the nausea and vomiting can be also on a physiologic or organic basis.

Summary

Every one of these sixteen patients was cured and the pregnancy carried on. It has not been necessary to perform a therapeutic abortion for hyperemesis in the Chicago Lying-in Hospital during the last few years. All staff cases and most of the private patients are treated by the routines outlined by Dieckmann.[7]

These observations reaffirm the need for proper controls in all clinical and therapeutic research just as it is necessary in the basic sciences. Since many factors can be involved in clinical studies, it does not become research until adequate and sufficient controls have been established.

A serious and earnest plea is advanced for critically controlled studies of all procedures and that publication be withheld until such controls are obtained.

Fortunately, pyridoxine can be given safely in these dosages (as far as we know now). Aside from the expense to the patient and delay in instituting therapy where cures did not follow, no particular damage can be claimed.

Another plea is offered for the retraction of prior recommendations when and as such corrections become evident to the original proponents.

Conclusion

Until factual evidence can be produced, it is proposed that pyridoxine in the dosages and methods used is of no more value in treatment of mild or moderate nausea and vomiting of pregnancy than scores of other preparations. On a percentage basis, better results were obtained by the administration of sterile water hypodermically and placebo tablets than by the use of pyridoxine. All the improvements can be explained readily on other bases.

The one patient with hyperemesis gravidarum of the entire series was cured only with the use of sedatives, and other measures. The use of pyridoxine as advocated in the literature for hyperemesis gravidarum is valueless and without justification.

This report does not imply that pyridoxine is not an essential vitamin but refers only to its use in the treatment of mild nausea and vomiting of pregnancy, as well as hyperemesis gravidarum.

The pyridoxine and the placebo material were supplied through the courtesy of the Department of Medical Research, Winthrop Chemical Company.

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SULFATHIAZOLE IN THE CONTROL OF EPIDEMIC DIARRHEA OF THE NEWBORN

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A NEW plague has been visited on the human race, and its victims are the newborn infants. In 1933 the first outbreaks of epidemic diarrhea struck the nurseries of maternity hospitals and caused tremendously high fatalities and spread consternation among the hospital staffs. The health authorities began an extensive study of the disease to determine its cause and to attempt to check it. A great deal of work and research have been done, but unfortunately the organism has not been found, nor has the source of infection been determined. Rules and regulations for the newborn nurseries have been formulated to help reduce the frequency of the outbreaks and to prevent the spread of the disease. But in spite of all rules and regulations being followed, and proper precautions being taken, the disease continues to recur. It evidently is a new disease which has come to stay and plague us and is much more prevalent than the published reports would indicate.

I will not go into all the phases of the disease as they have already been well described and those who have seen cases are familiar with its manifestations and are profoundly impressed with its seriousness. However, some doctors are totally unaware of the existence of this disease, so when they encounter the condition, they fail to realize its seriousness and thereby delay in instituting proper treatment, with the most serious consequences.

The treatment usually employed in diarrhea of childhood is not sufficient to check epidemic diarrhea, and to depend on it only delays the more effective treatment. I wish to stress here only one phase in the treatment of epidemic diarrhea. There is an adage which says, "God is good. He provides the remedy with the disease." This aptly applies to sulfathiazole and epidemic diarrhea of the newborn, as both have arrived about the same time. We have been using sulfathiazole with amazingly good results and consider it an almost specific remedy in this condition. The reason for its effectiveness in our cases is that we give the drug immediately at the first sign or symptom of the diarrhea.

This type of diarrhea quickly causes dehydration, great loss of weight, acidosis, and a general upset in the metabolism of the infant which soon becomes irreversible. To give the drug after this stage is apparently not as effective and cannot undo the damage already done, whereas if the sulfathiazole is given early and promptly, it halts the disease before any damage is done, and the infant remains well.

In the best-regulated hospitals and with all necessary precautions taken, the disease still breaks out. Now, with the shortage of help and the overcrowding due to the war situation, it is inevitable that the disease should be more prev-

alent. Or, the disease may have seasonal variations as do other contagious diseases of childhood, which may account for the present (1944-1945) increase. The fact remains that the disease is with us, and until we have more specific knowledge how to prevent an outbreak, we must use the best means available for its treatment.

Our nursery nurses are constantly on the alert for frequent or watery stools and have orders to report the condition to the house doctor immediately. The nurse has instructions to give the baby a dose of sulfathiazole from a stock solution even before the doctor arrives. The doctor then confirms the diagnosis and gives further orders. The stock solution we use is made up 1 grain to the teaspoonful (0.06 Gm. to 4 c.c.). The sulfathiazole is repeated, 1 grain every three hours. It is given with a medicine dropper or a teaspoon directly into the baby's mouth to assure that the baby gets the full dose. After only a few doses the diarrhea is usually under control without even changing the formula. If the diarrhea is not under control, then all food is withheld for about twelve hours and saline is given by clysis while the medication is continued. If a second case appears, the same treatment is given to that child. Besides, every baby in the nursery who has been exposed is given a dose (1 grain) of sulfathiazole as a prophylactic measure to prevent the spread of the disease.

If a baby who is ready to go home develops a loose or suspicious stool, a dose of the sulfathiazole is given to the baby, and the mother is given a bottle (60 c.c.) of the medicine to take home, with instructions to give the baby one teaspoonful every three hours. To insure that it takes the entire amount, the medicine is given in only one ounce of the formula and the rest of the formula is given afterwards. When a mother and baby leave the hospital, the mother is instructed to watch the stools and to telephone the hospital and her private physician if at any time frequent or watery stools occur. In this way we are forwarned of any outbreak of the disease and can institute treatment of the baby immediately and take necessary precautions at the nursery. To make certain that there is no delay in starting treatment, we have a member of the family come to the hospital for the medicine, and we instruct her how to give it, or we telephone to their druggist to make up the prescription. We consider the promptness in starting the treatment of the utmost importance and therefore do everything possible to avoid delay in treatment. The diarrhea is brought under control in less than twenty-four hours, and it is a relief to get a report that the baby is constipated. Whatever changes in the formula are made or not made are of secondary importance to the giving of the sulfathiazole promptly.

When treatment was not instituted promptly in the manner outlined, as happened when the diarrhea started at home and the family failed to notify us, or the doctor failed to recognize the condition, the baby developed all the classical symptoms of epidemic diarrhea with serious consequences. These incidents served as controls, demonstrating that the other cases which were checked by sulfathiazole would have developed similar symptoms.

We have not used sulfadiazine in epidemic diarrhea as we are reluctant to try anything else since sulfathiazole has served us so well. We have not had occasion to try penicillin.

By the above procedure we were able to control the diarrhea in the infants and prevent the disease from becoming epidemic in our nursery.

Summary

Sulfathiazole given promptly at the very onset of epidemic diarrhea in the newborn infant cures the disease in less than twenty-four hours and prevents its spread in the newborn nursery.

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1831 Grand Concourse

SULFANILAMIDE AND SULFATHIAZOLE ABSORPTION VIA RECTUM AND VAGINA

Further Studies

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WITH THE TECHNICAL ASSISTANCE OF
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RECENTLY there was reported from our laboratory a study[1] of sulfanilamide absorption via the vagina and rectum when the drug was given as a dry powder in a single weighed dose at the completion of operation on those viscera. In that study a constant amount of the drug, 5.9 Gm. (90 grains), was used in each case. Absorption was found to be fairly dependable but variable. We stated in that communication that it was our clinical impression that patients receiving the drug averaged a smoother convalescence than those who did not get it. We also felt that the presence of the drug in the vagina added a safety factor for patients having total hysterectomies, whether by the vaginal or abdominal route.

The known greater potency of sulfathiazole against some organisms made it desirable to study that drug also. Sulfanilamide had the generally better reputation in wounds and in the peritoneal cavity because of its lesser tendency to cake and lump in those localities, but we did not know how sulfathiazole would act in the rectum or vagina. There had also been considerable use by various surgeons of a mixture of sulfanilamide and sulfathiazole in wounds and in the peritoneal cavity. We did not know of any studies concerning the absorption of sulfathiazole or a mixture of the two sulfonamides from the vagina and rectum. We were interested also in determining whether the amount of sulfonamide used in the previous study was the optimum. It had been adopted as a safe initial twenty-four-hour dose on the basis of approximately 1 Gm. or 15 grains every four hours for six doses. Finally, we wondered how absorption from these viscera would compare with absorption from some enclosed area such as the peritoneal cavity. We were quite sure that, as a rule, not all of the drug was being absorbed from either viscus in our studies. The variations were so great that we did not wish to run the risk of too high concentration in the occasional patient by whom it was rapidly absorbed. Consequently we decided to check the vaginal and rectal absorption against the peritoneal as presumably all the drug would be absorbed from the peritoneal cavity.

From the new study, the following questions about the use of these two sulfonamides in the rectum and vagina were formulated:

1. How does absorption of sulfanilamide from the vagina and rectum compare with the absorption from the peritoneal cavity?

2. Does the absorption of sulfanilamide vary in proportion to the amount of drug used in the rectum and vagina?

3. Is sulfathiazole absorbed in similar manner from these viscera?

4. How is a mixture of these two sulfonamides absorbed?

5. What effect does the physical state of the drugs, i.e., whether introduced as a dry powder or as a paste, have upon their absorption?

The sulfanilamide determinations were run with the La Motte sulfonamide outfit.

The sulfanilamide and sulfathiazole mixed were determined with 0.15 c.c. of blood. This gave the same percentage as the determination of each sulfonamide separately as found by previous tests.

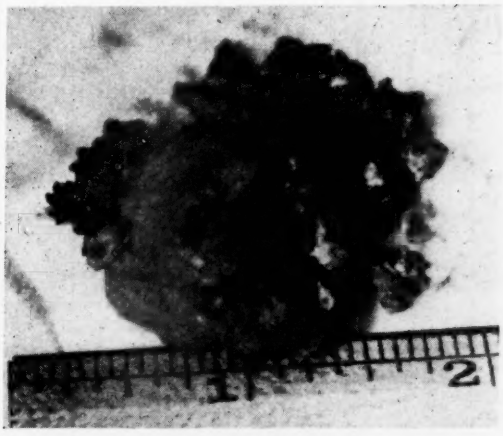

Fig. 1.—Hard cake of mixed sulfanilamide and sulfathiazole removed from the vagina fifty-six days after a mixture of the dry powders had been placed in the vagina at operation.

Question 1.—How does absorption of sulfanilamide from the vagina and rectum compare with its absorption from the peritoneal cavity?

Table I, when compared with our previous findings, showed a definitely higher and more constant level of the drug in the blood after intraperitoneal use than after rectal or vaginal administration.

Question 2.—Does the absorption of sulfanilamide vary in proportion to the amount of drug used?

Table II shows that within the limits of the previously recognized variations of absorption, the blood levels of the drug do vary directly with the amount of the dry powder placed in the rectum.

Table III, however, reveals a different story concerning vaginal absorption. Here, when the amount of dry drug was increased, the blood levels were less during the first two days after operation. Later, there was a rise as compared with the findings in our previous study when less drug had been used. Apparently moisture was the factor concerned. With more of the dry drug there was not sufficient moisture to get it into solution for early absorption.

Question 3.—Is sulfathiazole absorbed in similar manner from these viscera?

Tables IV and V show that a similar variable absorption of sulfathiazole takes place from the rectum and vagina. The blood levels do not appear significantly different from those obtained when using sulfanilamide.

Question 4.—How is a mixture of these two sulfonamides absorbed?

Tables VI and VII show that mixing the drugs appears to have little effect upon their absorption, though the blood level after rectal administration was somewhat less than for either of the drugs when given singly.

TABLE I. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER INTRAPERITONEAL ADMINISTRATION

HOSP. NO.	WT. (LB.)	DRUG ADMINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	DAYS 2	3	4	5	6	7	8	9
22029	197	Sulfanilamide	paste	9	Abdomen	9	4.5	4	Tr.	2					
22041	172	Sulfanilamide	paste	11.2	Abdomen	7	4	1.5	2	1.5	1.5	1.5	2.5	Tr.	Tr.
22108	154	Sulfanilamide	paste	5.8	Abdomen	3	1.5	Tr.	3	Tr.	Tr.	3	Tr.	2.2	Tr.
22096	114	Sulfanilamide	paste	5.8	Abdomen	3	2	Tr.	3	0					
22103	153	Sulfanilamide	paste	5.8	Abdomen	8	3	Tr.	Tr.						
22126a	117	Sulfanilamide	paste	5.8	Abdomen	4	2	0							
22396	179	Sulfanilamide	paste	8.4	Abdomen	Tr.	1.3	0	2.6	2.6	5.2	1.9	1.9	1.3	0
22420	150	Sulfanilamide	paste	5.8	Abdomen	6	0	5	2	0					
	Average			6.2		5	2.3	1.3							

In the tables the blood findings are reported in milligram per cent (mg. %) of sulfanilamide. Periods left blank mean that no tests were made at those times. "0" means that blood tests were done and failed to show any sulfanilamide present. "Tr." means trace present in insufficient amount for accurate determination—approximately less than 0.5 mg. per cent.

TABLE II. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER RECTAL ADMINISTRATION AS A DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG ADMINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	DAYS 2	3	4	5	6	7	8	9
22004	92	Sulfanilamide	powder	5.8	Rectum	6	6	4	5	0.5					
21992	160	Sulfanilamide	powder	11.2	Rectum	12	3.5	3.5	3.5	Tr.					
22001	118	Sulfanilamide	powder	5.8	Rectum	2	1	0.5	1	Tr.	Tr.	Tr.			
22014	174	Sulfanilamide	powder	11.2	Rectum	1	3	3	1	Tr.					
22030	120	Sulfanilamide	powder	9	Rectum	3	4	2	1	Tr.	1	Tr.			
	Average			8.6		5.8	3.5	2.8	2.3						

TABLE III. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER ADMINISTRATION AS DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG ADMINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	DAYS 2	3	4	5	6	7	8	9
22008	165	Sulfanilamide	powder	11.2	Vagina	0.5	5.5	3	Tr.	Tr.	1.5	Tr.			
22013	150	Sulfanilamide	powder	11.2	Vagina	0.5	1	Tr.	3	Tr.	2	Tr.			
22024	118	Sulfanilamide	powder	7	Vagina	Tr.	Tr.	Tr.	3	1.5	Tr.	1	Tr.	2	Tr.
22187	92	Sulfanilamide	powder	5.8	Vagina	0	0	1.5	1.5	1.5	1.5	0			
	Average			8.8		0.25	1.4	1.1	1.6						

TABLE IV. SULFATHIAZOLE CONCENTRATION IN BLOOD AFTER RECTAL ADMINISTRATION AS A DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG ADMINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	DAYS 2	3	4	5	6	7	8	9
22023	200	Sulfathiazole	powder	8	Rectum	1.5	4.5	5.2	1.5	4.5	2.2	Tr.			
22035	96	Sulfathiazole	powder	5	Rectum	3	9.6	Tr.	1.5	3	2.5	1.5			
22078	152	Sulfathiazole	powder	5.8	Rectum	Tr.	1	Tr.	Tr.	Tr.	1	0	1.5		
22125	175	Sulfathiazole	powder	9	Rectum	Tr.	5.9	Tr.	2.2	0					
22138	219	Sulfathiazole	powder	8.4	Rectum	Tr.	1.5	1.5	0.7	2.2	0		0		
22150	155	Sulfathiazole	powder	5.8	Rectum	0	0	0	0						
22158	145	Sulfathiazole	powder	5.8	Rectum	Tr.	0	1.4	0						
22166	141.5	Sulfathiazole	powder	5.8	Rectum	Tr.	0	0							
22180	141.5	Sulfathiazole	powder	5.8	Rectum	Tr.	0	0							
	Average			6.6		0.5	3.5	0.9							

TABLE V. SULFATHIAZOLE CONCENTRATION IN BLOOD AFTER VAGINAL ADMINISTRATION AS DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG ADMINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	DAYS 2	3	4	5	6	7	8	9
22022	114	Sulfathiazole	powder	6	Vagina	4.4	1.5	Tr.	Tr.	Tr.	Tr.	1.5	Tr.		
22064	123	Sulfathiazole	powder	5.8	Vagina	Tr.	Tr.	Tr.	Tr.	0					
22122	178	Sulfathiazole	powder	8.4	Vagina	1.5	Tr.	0	0						
22129	154	Sulfathiazole	powder	8.4	Vagina	5.9	0	0							
22135	163	Sulfathiazole	powder	5.8	Vagina	1	0	Tr.	Tr.						
22143	165	Sulfathiazole	powder	8.4	Vagina	Tr.	0		0						
22155	125	Sulfathiazole	powder	5.8	Vagina	Tr.	0	0.7							
	Average			6.9		1.8									

TABLE VI. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER RECTAL ADMINISTRATION OF EQUAL PARTS OF SULFANILAMIDE AND SULFATHIAZOLE AS A DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG ADMINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	DAYS 2	3	4	5	6	7	8	9
22243	140	Sulfanilamide Sulfathiazole	powder	5.8	Rectum	1.5	2.3	3	0						
22270	183	Sulfanilamide Sulfathiazole	powder	8.4	Rectum		0	1.5	0						
22354	150	Sulfanilamide Sulfathiazole	powder	5.8	Rectum	1	0	0							
22359	102	Sulfanilamide Sulfathiazole	powder	5.8	Rectum	1.5	Tr.	0	2	2.5	2				
22410	205	Sulfanilamide Sulfathiazole	powder	8.4	Rectum	2	1	1	0.5	4	0				
22408	135	Sulfanilamide Sulfathiazole	powder	5.8	Rectum	1.5	1	1.5	0	6	1.5				
Average				6.7		1.25	0.7	1.1							

TABLE VII. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER VAGINAL ADMINISTRATION OF EQUAL PARTS OF SULFANILAMIDE AND SULFATHIAZOLE AS A DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG ADMINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	DAYS 2	3	4	5	6	7	8	9
22192	143	Sulfanilamide Sulfathiazole	powder	5.8	Vagina	5	1	0.5	0						
22151a	143.5	Sulfanilamide Sulfathiazole	powder	5.8	Vagina	0.5	0	0							
22350	165	Sulfanilamide Sulfathiazole	powder	8.4	Vagina	0	1	0	0						
22353	135	Sulfanilamide Sulfathiazole	powder	8.4	Vagina	1	1	0	0						
22385	133	Sulfanilamide Sulfathiazole	powder	5.8	Vagina		1	0	0						
22387	115	Sulfanilamide Sulfathiazole	powder	8.4	Vagina	1	0	0							
22356	122	Sulfanilamide Sulfathiazole	powder	8.4	Vagina	2	2.4	2	2	1.5	2	2.5	0.5	0	0.5
22371	130	Sulfanilamide Sulfathiazole	powder	5.8	Vagina	4	4	2	1.5	1	0	0	3	1	1.5
22406	148	Sulfanilamide Sulfathiazole	powder	5.8	Vagina	3	2	1	2	0.5	3.5	0.5	2	1.5	0.5
Average				6.9		1.3	1.3								

TABLE VIII. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER RECTAL ADMINISTRATION OF EQUAL PARTS SULFANILAMIDE AND SULFATHIAZOLE AS A PASTE

NO. HOSP.	WT. (LB.)	DRUG ADMINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	DAYS 2	3	4	5	6	7	8	9
22544	160	Sulfanilamide Sulfathiazole (paste)	paste	8.4	Rectum	6	2.5	2	1.5	3	1.5	2			
22560	146	Sulfanilamide Sulfathiazole (paste)	paste	5.8	Rectum	3.5	2	2.5	1.5	2.5	1.5				
	Average			7.1		4.7	2.2	2.2							

TABLE IX. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER VAGINAL ADMINISTRATION OF EQUAL PARTS OF SULFANILAMIDE AND SULFATHIAZOLE AS A PASTE

HOSP. NO.	WT. (LB.)	DRUG ADMINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	DAYS 2	3	4	5	6	7	8	9
22443	100	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	1.5	1	1	0.5	1	1	0			
22444	129	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	1.5	1	1	1	Tr.	1.5	0	0		
22450	148	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	4.5	1	0.5	0	1	0	0			
22445	155	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	1	1	1	Tr.	1	0	0			
22468	119	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	1	1		0	0					
22526	128	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	3	2	1.5	1	0	2	2	1	1.5	1
22538	155	Sulfanilamide Sulfathiazole	paste	8.4	Vagina	1.5	1.5	0	2	1.5	1	1.5	1.5	2	2
22552	100	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	1.5	1.5	1.5	2	1.5	2.5	0.5	1.5	0.5	1.5
22561	125	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	1	1.5	1.5	1	2.5	1.5	1	2.5	0.5	1
22589	150	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	2.5	3	1	1						
22580	100	Sulfanilamide Sulfathiazole	paste	5.8	Vagina	2	2.5	1.5	2						
	Average			6.36		1.6	1.55	1	0.8						

Question 5.—What effect does the physical state of the drugs, i.e., whether introduced as a dry powder or as a paste, have upon their absorption?

Tables VIII and IX, when compared with Tables VI and VII, indicate that the mixed drugs are definitely better absorbed when introduced into the vagina or rectum as a moist paste than they are when introduced as a dry powder.

It should be noted in this connection that a mixture of equal parts of sulfanilamide and sulfathiazole goes through an interesting process as water is added to it. It gradually becomes moist and looks as though it were going to form a paste. Then it rather suddenly stiffens up and resembles partially set plaster. After a little more water has been added it again becomes a soft, moist paste. From one patient into whose vagina a mixture of the dry powders was placed at operation, a firm cake was removed when she returned for checkup eight weeks later (Fig. 1). Her blood had shown a minimal absorption of the drug. (See History No. 22353, Table VII.) The powders in this case had evidently been moistened only sufficiently to get to the plaster stage.

Since completion of this study, we have used these drugs vaginally in the treatment of a few cases of gonorrheal infection with excellent results. Our contact with such cases is rather limited but on theoretical grounds the vaginal use should give higher local concentration than would be obtained with similar blood levels after oral administration.

Summary

Sulfanilamide and sulfathiazole, separately or together, are absorbed variably from the rectum and vagina.

The absorption is hastened when the drug is inserted as a moist paste.

A mixture of the two drugs should be moistened beyond the "plaster" stage when used in the vagina.

It is suggested that local gonorrheal infections in women might be treated advantageously with sulfonamides via the vagina.

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ARE ANTIHORMONES FORMED DURING PREGNANCY?

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IT IS well known that antigonadotrophins may form in the blood stream of patients to whom gonadotrophic therapy has been administered.[1] However, these therapeutic measures frequently involve the injection of extracts of heterologous source and thus the formation of antagonistic substances might be anticipated. An unusual situation is created by pregnancy for during this time there is a marked and continuous production of chorionic gonadotrophin and, while this substance is of homologous source, it is nevertheless adding a new substance to the blood stream. Optimal conditions for the spontaneous development of antihormones are presented by pregnancy, and limited tests have been made during this period and up to one month after parturition for the detection of antagonists in the serum against pregnancy urine extracts, but all were negative.[2-5] Extended treatment of patients with chorionic gonadotrophin has also failed to cause antihormone formation. For example, Dorff[6] administered as much as 112,300 R.U. over a seventeen-month period and during this time antigonadotrophins did not appear.

Although it would appear that antihormones against pregnancy urine extracts do not develop during pregnancy, the fact that a prolonged amenorrhea occurs in some cases following parturition led us to reinvestigate the antihormone problem. It seemed more logical to consider the formation of antagonists against the pituitary as a possible etiology of the amenorrhea. Fluhmann[2] did test postpartum serum against human pituitary in one case but failed to detect antihormones. Therefore, in view of the paucity of data concerning the antihormone formation during pregnancy we are presenting the data from ten cases in which the sera were tested for antigonadotrophins against both chorionic gonadotrophin and human pituitary.

Procedures and Results

Blood was obtained from 8 patients four weeks post partum and from 2 patients two weeks post partum. The blood was permitted to clot, the serum separated, centrifuged, and stored in an ice chest until and during the test period. All sera tests were started within seventy-two hours after the blood was drawn.

To test for antihormones against chorionic gonadotrophin, 22-day-old female mice were used. All test mice received a total of 40 I.U. of chorionic gonadotrophin in equally divided daily doses and, at a different site, a total of 0.9 c.c. of the serum to be tested. Injections were made subcutaneously once daily for three days and the mice killed seventy-two hours after the first injection. The weights of the ovaries and uteri were obtained at autopsy, the later after removal of intrauterine fluid. Two to four mice were used for each serum test and this response was compared with two litter mates injected with chorionic gonadotrophin alone.

TABLE I. ANTIGONADOTROPHIC TESTS IN MICE WITH POSTPARTUM SERA

SERUM FROM PATIENT	CHORIONIC GONADOTROPIN (I.U.)	SERUM (C.C.)	AVERAGE OVARIAN WT. (MG.)	AVERAGE UTERINE WT. (MG.)
E. G.	40	0.9	7.2	29
V. B.	40	0.9	10.3	27
C. J.	40	0.9	8.2	30
D. H.	40	0.9	9.3	27
B. W.	40	0.9	8.9	31
A. B.	40	0.9	9.9	30
E. W.	40	0.9	7.5	17
E. S.	40	0.9	7.5	29
H. D.	40	0.9	8.1	46
R. H.	40	0.9	8.7	47
Control Experiments				
	40	None	8.8	34
	None	None	3.0	6

Antihormone tests for antagonists against human pituitary were performed in the manner described but in this case 22- to 24-day-old rats were used instead of mice. The human pituitary material was acetone dried and administered in 2 mg. quantities. The pituitary powder was macerated in a centrifuge tube with a small amount of distilled water and after making the desired dilution was injected as an extract and suspension. The 2 mg. dosage produced a marked and uniform ovarian stimulation.

An inhibitory serum can readily be detected by its ability to nullify the gonad-stimulating capacity of a uniform dose of a gonadotrophic hormone. Table I illustrates that none of the ten sera examined gave reason to suspect the presence of antihormones against chorionic gonadotrophin. A marked increase in ovarian weight resulted with the dosage of hormone used and this stimulating action was not influenced by the simultaneous administration of postpartum serum. Similar results were obtained with human pituitary. A pronounced ovarian weight increase was obtained with the human pituitary material but the gonadotrophic activity was not impaired by concomitant serum administration. (Table II.)

TABLE II. ANTIGONADOTROPHIC TESTS IN RATS WITH POSTPARTUM SERA

SERUM FROM PATIENT	HUMAN PITUITARY (MG.)	SERUM (C.C.)	AVERAGE OVARIAN WT. (MG.)	AVERAGE UTERINE WT. (MG.)
E. G.	2	0.9	53	76
V. B.	2	0.9	120	112
C. J.	2	0.9	50	82
D. H.	2	0.9	64	155
B. W.	2	0.9	71	115
A. B.	2	0.9	57	89
E. W.	2	0.9	69	80
E. S.	2	0.9	70	150
H. D.	2	0.9	55	117
R. H.	2	0.9	62	181
Control Experiments				
	2	None	61	111
	None	None	13	32

In agreement with previous reports, therefore, we did not find antihormones against chorionic gonadotrophin in postpartum serum. Furthermore, our tests for antigonadotrophins against human pituitary were negative. On the basis of the evidence at hand we cannot subscribe to an antihormonic cause for amenorrhea following parturition. We have used 0.9 c.c. of serum

routinely in testing for antihormones and this amount can be contested as insufficient. However, previous experience has indicated that definitely inhibitory sera can readily be detected with the 0.9 c.c. quantity.[7, 8]

Summary

The sera from 10 patients, two to four weeks postpartum, were tested for the presence of antigonadotrophic substances against chorionic gonadotrophin and human pituitary. All tests were uniformly negative. Thus gonadotrophins of homologous source are not antigenic and no evidence is available for an antihormonic cause of amenorrhea following parturition.

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ETHINYL ESTRADIOL IN THE TREATMENT OF METRORRHAGIA

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THE induction of cyclic bleeding in the anovulatory type of metrorrhagia by the cyclic administration of estrogen-progesterone was originally advanced by Hamblen.[1] His observation that the functional bleeding of adolescence could be satisfactorily controlled by the administration of the estrogens was subsequently confirmed by this author, who reported upon the use of cyclic stilbestrol-progesterone in the treatment of these patients.[2] The evidence is now adequate to permit a dogmatic statement on the efficacy of the estrogens in the control of functional bleeding. So specific is the administration of the estrogens in large doses, that complete cessation of uterine bleeding may be expected in approximately 80 per cent of the patients with anovulatory functional bleeding within a period of seventy-two hours, following the daily administration of stilbestrol (5 mg.) every twenty-four hours. A serious objection to the use of such large doses of stilbestrol is to be found in the high incidence of nausea which it produces. It is a tragic sequence when a patient, being already partially exsanguinated, is unable to receive benefit of therapy because of her failure to tolerate the drug. A second objection to stilbestrol therapy is based on the fact that it is a sterol derivative whose chemical structure has little similarity to estradiol. On purely hypothetical grounds, it would seem that the administration of an estrogen chemically akin to that which the human body is accustomed to metabolize should be more acceptable. Until a recent date the natural estrogens and the synthetic estradiols were available for oral administration in a dosage form which made them practical for the treatment of the climacteric where small doses are adequate, but totally impractical for the control of metrorrhagia where large oral doses are necessary. A synthetic estrogen, chemically similar to natural estrogen and sufficiently potent when administered orally, has been made available in the form of ethinyl estradiol. It has been shown by Willard Allen that this estrogen is 26 times as potent as hexestrol, and 7.5 times as potent as diethylstilbestrol.[3]

Clinical Material Comprising Study

In order to compare the hemostatic effect of ethinyl estradiol with previous experience using diethylstilbestrol, a group of twelve patients suffering with anovulatory functional bleeding were studied. All of these patients were partially exsanguinated from prolonged, intermittent, uterine bleeding, the hemoglobin ranging from 24 per cent (Sahli) to 60 per cent. From each patient, an endometrial biopsy was obtained before starting treatment. In each case, the endometrium showed a persistent proliferative phase which varied from moderate atrophy to marked hyperplasia. The degree of endometrial atrophy or hyperplasia is not necessarily related to the amount or duration of bleeding.

Careful examination of these case reports will reveal that the most persistent uterine bleeding is found in those cases with atrophy of the endometrium, while those with hyperplasia are more readily controlled. In each of these patients, the endometrial biopsy was repeated at intervals of one week for periods of time varying from two weeks to five weeks. Another biopsy was obtained upon completion of the treatment, and in seven cases a follow-up biopsy was taken six months after completion of all treatment. The average number of endometrial biopsies for the entire group was six per patient. At the same time that each endometrial biopsy was taken, a vaginal smear was obtained by aspiration and stained for study of the glycogen content and degree of keratinization of the vaginal epithelium.

Treatment Program

Following the confirmation of diagnosis by endometrial biopsies, all patients were placed on the same treatment program. They were given a 0.3 mg. of ethinyl estradiol (6 tablets of 0.05 mg. each) daily at bedtime for twenty nights. On each of the last five days of the ethinyl estradiol, each patient also received 5.0 mg. of progesterone by hypodermic injection. Both ethinyl estradiol and progesterone treatment were discontinued on the twentieth day, and in every case of estrogen-progesterone withdrawal, bleeding occurred within one to six days after cessation of treatment. On the fifth day from the onset of this induced bleeding episode, the twenty-day treatment of ethinyl estradiol, supplemented by progesterone on the last five days, was repeated. Again, all treatment was stopped, and a third cycle of treatment was instituted. In other words, after the bleeding had been controlled by twenty days of estrogen-progesterone treatment, and the induced bleeding episode had occurred, then the patients were instructed on printed instruction sheets to take six tablets daily at bedtime from the fifth to the twenty-fifth day of the menstrual cycle. They were instructed to come to the clinic on the twentieth, twenty-first, twenty-second, twenty-third, and twenty-fourth day of their cycle for an injection of progesterone. (All cases are not reported in detail because of the paper shortage which necessitates editorial limitation.) A typical case is reported:

M. R. B., aged 16 years.

April 8, 1944.—Menses began at 12 years of age, followed by several scanty menses at long intervals over a period of two years; during the last year, menstrual periods averaged from three to five weeks in duration. Flow has never been excessive in amount, but the duration has been such as to make it necessary for the patient to wear a pad most of the time. Endometrial biopsy: Hyperplastic proliferative phase; tendency to polypoid formation. Vaginal smear: 4 + keratinization; 1 + superficial cells; no basal cells; no leucocytes; 4 + blood.

April 17, 1944.—Bleeding has persisted since last examination. Endometrial biopsy: polypoid hyperplastic proliferative phase. Vaginal smear: 4 + keratinization; 1 + superficial cells; 4 + blood. Twenty-day treatment of ethinyl estradiol plus progesterone started.

May 1, 1944.—All bleeding stopped after the third day of treatment. Slight nausea occurred as a result of ethinyl administration. Patient was made to persist in taking it. Endometrial biopsy: polypoid hyperplastic proliferative phase. Vaginal smear: 4 + keratinization; 1 + superficial cells; no blood; no leucocytes.

May 6, 1944.—Treatment stopped.

May 11, 1944.—Menstruation began. Flow was normal in amount. No dysmenorrhea.

May 15, 1944.—Ethinyl-estradiol-progesterone twenty-day treatment resumed.

June 4, 1944.—Treatment stopped.

June 6, 1944.—Menstruation began, normal in amount and duration. Endometrial biopsy: secretory phase. Vaginal smear: 4 + keratinization; no superficial cells; no basal cells.

This patient was followed over a period of four months after completing three cycles of treatment, and she continued to have normal cyclic uterine bleeding. Each endometrial biopsy showed a normal secretory phase. One cannot attribute to therapy the transition of this patient from the anovulatory to the ovulatory because this may have been the result of normal physiologic maturity not related to the treatment.

Summary

Irregular bleeding, acyclic bleeding from the uterus, must first be classified according to etiology. Approximately one-half of the patients seen in private practice with this complaint have an organic basis for that bleeding. The other half bleed from the uterus as a result of abnormal physiology in the pituitary-ovarian endometrium cycle. This latter group must be further classified into two groups. Those who bleed from a secretory phase endometrium are essentially normal endocrinologically in that the prime prerequisite for normalcy is present, namely, the maturation of the follicle with the extrusion of the ovum and development of the corpus luteum, followed by normal endometrial response. The patients in whom the bleeding comes from a proliferative phase endometrium are candidates for treatment by endocrine therapy.

Bleeding can be controlled satisfactorily by the administration of large oral doses of the estrogens. Use of estrogen-progesterone over a period of three successive months will establish regular cyclic bleeding in about 90 per cent of anovulatory metrorrhagic patients while under treatment. Normal cyclic menstruation will continue in about 70 per cent of patients after discontinuing treatment. Of this latter group, about one-half of them will subsequently menstruate from a secretory phase endometrium, suggesting that the treatment not only controls the immediate bleeding, but may also establish normal, pituitary-ovarian-endometrial physiology. In that group which ovulates following treatment, it is obviously impossible to state that the ovulation was induced by therapy, since spontaneous recovery of ovarian function can occur in the absence of any treatment. However, the relatively high salvage in this group of cases of marked ovarian failure suggests the probability of a cause and effect relationship.

Summary and Conclusions

Ethinyl estradiol (0.3 mg.) was administered daily for twenty days to a group of twelve patients suffering from anovulatory metrorrhagia; the treatment was begun as soon as the diagnosis was established. All of these patients were partially exsanguinated from prolonged and excessive bleeding. Uterine bleeding stopped in all cases except one within six days after starting treatment. Progesterone (5 mg.) was administered daily by hypodermic injection on the last five days of ethinyl estradiol administration. When the ethinyl estradiol-progesterone twenty-day treatment was stopped, all patients menstruated within five days as a result of estrogen-progesterone withdrawal. On the fifth day from the onset of this induced bleeding episode, the twenty-day treatment was resumed, and another bleeding episode occurred in all patients within five days after completing the second cycle of treatment. A third cycle of treatment was instituted on the fifth day of this bleeding episode. In other words, the patients

were treated from the fifth to the twenty-fifth day of the menstrual cycle by ethinyl estradiol (0.3 mg.) daily for 20 days, and progesterone (5 mg.) from the twenty-first to the twenty-fifth day of the menstrual cycle. All of these patients were followed by repeated endometrial biopsies and vaginal smears during the treatment. A follow-up of from three to twelve months after treatment was presented.

Ethinyl estradiol in oral dose of 0.3 mg. is comparable to diethylstilbestrol in oral dose of 5 mg. in so far as control of anovulatory bleeding is concerned. Only one patient complained of nausea from the ethinyl estradiol, and this was not troublesome. The incidence of regular cyclic bleeding following ethinyl estradiol is about the same as in a previously reported group treated with diethylstilbestrol. However, the ovulation salvage in the ethinyl estradiol group (35 per cent) was distinctly better than that in the diethylstilbestrol treated group (16 per cent).

Estinyl (ethinyl estradiol) and progesterone (proluton) supplied through the courtesy of Dr. William R. Bond of the Schering Corporation.

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PUERPERAL STERILIZATION

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DURING the past four years 51 puerperal sterilizations have been performed on the obstetric services at the Sloane Hospital for Women. This small group of cases will be reviewed and compared with the ten series of similar cases reported in the American literature up to December, 1944.

Skajaa[1] was one of the earliest advocates of puerperal sterilization. In 1932 he reported on 46 cases. In 1939 Adair and Brown[2] reviewed 50 cases, the first series to appear in the American literature. Since then ten additional series have been reported.[3-12]

The first puerperal sterilization at Sloane Hospital was performed in 1938. Since then the number of such operations has increased every year as follows:

		1941	6
1938	1	1942	10
1939	1	1943	10
1940	6	1944	17

The number of viable births in 1942, 1943, and 1944 was 1,680, 1,859, and 1,964, respectively. Our incidence of postpartum sterilizations in terms of viable births for these three years was 0.59 per cent, 0.54 per cent, and 0.85 per cent. Our indications for performing this operation follow closely those outlined by others.[2, 8, 9] Table I lists the indications. By multiparity we include only those patients having three or more living children at the time of performing this operation. The entire group had a total of 186 living children out of a total of 299 pregnancies.

Their ages ranged from 21 to 42 years. The average was 32.8 years.

The Pomeroy sterilization was used exclusively.

The average follow-up for all patients operated on prior to 1944 was 14.7 months.

The one known failure in this series has been reported in another communication.*

The operations were performed between the first and the tenth postpartum days. The distribution and morbidity rate, based on the standards set by the Committee on Maternal Welfare, are shown in Table II. Twenty-three, or 46 per cent, of the patients were entirely afebrile throughout their puerperium.

Postoperative complications included two cases of thrombophlebitis, one severe upper respiratory infection, one nonfatal pulmonary embolism, one hematoma of the broad ligament, one minor wound infection, and one wound hematoma.

*AM. J. OBST. & GYNEC. (later issue).

TABLE I. INDICATIONS FOR PUERPERAL STERILIZATION

Rheumatic heart disease	9
Recurrent toxemia	9
Recurrent pyelonephritis	2
Multiparity	35
Epilepsy	2
Recurrent hyperemesis	2
Bronchiectasis	1
Poliomyelitis deformity	1
Psychosis	3
Tertiary syphilis	1
Hypertension	3
Hypertrophy of breasts	1
Congenital cystic disease of lungs	1
Multiple sclerosis	1
Erythroblastosis, recurrent	1

TABLE II. PUERPERAL STERILIZATIONS, TIME OPERATION PERFORMED AND MORBIDITY

DAY OF OPERATION	NO. OF PATIENTS	NO. FEBRILE	PER CENT
1	1		
2	2		
3	12	3	25.0
4	16	3	18.7
5	10	3	30.0
6	6	1	16.6
7	1		
8	1		
9	1		
10	1		
Total	51	10	19.7

No routine type of anesthesia was used in this series. Pentothal sodium intravenously, nitrous oxide with oxygen and ether, and local novocain were used, depending on the patient's medical condition.

A short vertical incision and absorbable suture material were used throughout.

In this series there were five medical inductions of labor. In ten cases the membranes ruptured before the onset of labor, two to twelve hours before delivery. Three low forceps deliveries were performed. There was one case of prolonged labor. In another patient manual removal of the placenta was necessary. One patient had a curettage and tamponade of the uterus on her fourth postpartum day because of retained secundines. This delayed postpartum sterilization until her tenth day. Only two of these cases were morbid, namely, one of the low forceps deliveries, and one patient who had a fifty-two-hour labor.

In six instances the resected tubal fragments revealed either a mild subacute or acute endosalpingitis. Only one of these patients was febrile.

The average period of hospitalization for these patients was about fifteen days.

Discussion

A survey of the reported series of puerperal sterilizations reveals many individual variations (Table III). Considerable discussion has revolved around the question of immediate or delayed operation. Skajaa[1] chose the third and fourth postpartum days as the optimal time for sterilization. Adair and Brown[2]

TABLE III

AUTHOR AND YEAR	AVERAGE AGE (YR.)	AVERAGE PARITY	TECHNIQUE	AVERAGE TIME OPERATION PERFORMED P.P.	PER CENT MORBIDITY	COMPLICATIONS	MATERNAL MORTALITY	FOLLOW-UP (%)	NUMBER OF CASES	FAILURES	ANESTHESIA	TOTAL HOSPITAL DAYS	INCIDENTAL SURGERY
Skajaa[1] 1932	37.1		Cornual resection	5 days		8 thromboses 1 embolism			126		114 local 12 ether		
Adair and Brown[2] 1939	29.5	4.6	Madlener	11.5 hours	12	6 thromboses	0		50	0	Local	11.3	
Russell[3] 1940		5		2 hours		1 abscess	0		29			10	
Amundsen[4] 1940	35.8	5.8	Cornual resection	5 days	10.8	6 thromboses			150	0	Local		
Hewitt and Whitley[5] 1940	31	5.5	Modified Madlener	1 hour	2	1 sepsis 1 pyelitis			100		General	9.4	
Pfuetze[6] 1941	27.8	5	Madlener	17.5 hours	18.3	2 phlebitis	0		165	3	Local	9.4	3 herniorrhaphies
Thornton[7] 1941	29.4	6.6 for 175 patients	219 Pomeroy 86 Resections 3 Madlener	5 days	21	3 endometritis 3 pyelitis 2 pneumonias 1 embolus 1 phlebitis 1 atelectasis 1 diabetic coma	1	73	309	0	297 spinals 9 general 3 local	11.7	178 appendectomies
Mays and Dilworth[8] 1941	28	5	29 Modified Madlener 2 Cornual	50% on 4th day	28	1 pneumonia 2 cystitis 3 endometritis 1 atelectasis	0		31		Local	16.7	
Birch[9] 1941	28.4	4.5	Resection	26 hours	2.8	2 wound infections			35		Local	9.5	
Brennecke[10] 1941			Madlener						23				
Lock[11] 1942		4.7	57 Pomeroy 2 Madlener		8.5	1 phlebitis 1 pyelitis 1 hematoma		54	59	2	Local	7.1 days after operation	1 appendectomy
Goldblatt[12] 1943			Pomeroy	3rd day	30						Local		
Sloane 1944	31.9	5.8	Pomeroy	4.5 days	21.2	2 phlebitis 1 embolism 1 wound hematoma 1 hematoma broad ligament	0	95	34	1	15 pentothal 19 gas-oxygen-ether	15.8	Excision 2 parovarian cysts

elected to perform their sterilization immediately after delivery. Others who believe in early operation include Pfuetze,[6] Russell,[3] Hewitt and Whitley.[5] Pfuetze had a morbidity rate of 13 per cent for cases operated on within the first twenty-four hours as compared with 30 per cent for those done later. Adair and Brown's morbidity was 12 per cent, and Hewitt and Whitley's, 2 per cent. Other authors do not believe that the time of performance of this operation has any bearing on the incidence of postoperative morbidity. Among these are Mays and Dilworth,[8] Goldblatt[12] and Thornton.[7] Their morbidity rates were 28 per cent, 30 per cent, and 21 per cent respectively. Thornton's series is the largest. He performed puerperal sterilizations up to three weeks after delivery and found no correlation between the time of performance of the operation and febrile reaction. Thornton believes that the careful selection of patients is far more important with reference to morbidity than when the sterilization is performed. In our small series of cases there was no definite trend in morbidity which seemed totally unrelated to the day on which the operation was performed (Table II).

Skajaa's high incidence of thrombophlebitis and embolism was surely related to his high incidence of intrapartum manipulation in the preceding labor. A more careful selection of cases would undoubtedly have lowered his high morbidity. Adair and Brown[2] and Thornton[7] emphasize the importance of this. However, it is inevitable that an occasional candidate for puerperal sterilization will develop some intrapartum complication necessitating either major or minor obstetric procedures. Whether or not such a procedure should contraindicate sterilization is a matter of judgment. Certainly, in such cases, one would be foolhardy in performing an early sterilizing operation without waiting a few days to determine whether or not she will develop an acute puerperal infection. Not a few cases of puerperal sepsis have followed perfectly normal labor and delivery. With these facts in mind it is our policy to perform this operation the fourth day when possible, by which time, in most cases, contraindications in the form of sepsis or endometritis will have become manifest.

The only advantage in early operation seems to be shortening of the patient's hospital stay. Our patients spent, on the average, fifteen days in the hospital. In many instances these patients had heart disease or toxemia which necessitated longer convalescence.

Of some interest is Thornton's 178 appendectomies, performed as incidental procedures at the time of puerperal sterilization. We do not feel that such a procedure is either indicated or justified. The only incidental surgery we performed was the removal of two parovarian cysts.

For the most part the type of anesthesia used seems to be a matter of personal preference. In our cases we used chiefly intravenous pentothal, or gas, oxygen, and ether.

Conclusions

1. Postpartum sterilization is a rational and safe procedure when indicated.

2. Cases for this procedure should be selected with care.

3. The fourth or fifth postpartum day is the safest time for performing this operation.

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PANHYSTERECTOMY WITHOUT VAGINAL CLEANSING*

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IN MANY gynecologic clinics special precautions are taken to cleanse and sterilize the vagina preliminary to panhysterectomy. Many operators have attributed the absence of operative infection in their cases to this procedure. In this clinic for many years it has been the practice to consider the vagina potentially infected and any complete sterilization impossible. Besides their presence in the vaginal secretions, organisms may be found below the surface between cells. The continuous extrusion of secretions from the cervix, and the peculiar anatomic configuration of the vagina with its many folds are some of the factors which make it impossible actually to sterilize the vagina.

Therefore, in this Clinic, abdominal panhysterectomies are performed without any vaginal preparation. Since we consider the vagina to be a septic focus, we believe it is wiser to adopt measures of isolation of the said focus rather than trust to a necessarily imperfect sterilization. The method we use to meet this aim will be made clear in the technique.

Technique of Operation

After anesthetization the patient is catheterized and re-examined vaginally to verify the preoperative diagnosis and the cervix is again inspected for pathology. No attempt whatsoever is made to cleanse or sterilize the vagina. Since clamps are not used, many of the operations are easily performed through a relatively small incision. We use the following method: Each vessel is doubly ligated, the ligatures are tied but are not cut. The catgut ends are brought out of the wound and held with hemostats; these can be used for traction in order to bring a bleeding vessel into better view if necessary in difficult cases. The ligaments and the bladder reflexion are then sectioned to uncover the uterine arteries. The bladder is pushed downward anteriorly and laterally below the cervix. The uterine vessels are then doubly ligated by passing the ligature carrier at right angles to the long axis of the uterus close to the cervix, at the level of the internal os, to avoid the ureters (Fig. 1). Moderate traction is made by an assistant on the ligatures of the uterine vessels while they are cut and pushed off the uterus with gauze.

The following technique to isolate the infected vagina is then applied meticulously; two sponges are placed in the cul-de-sac. A small incision is then made in the anterior fornix just above the palpated end of the cervix. An assistant immediately places an Allis forceps on the cut anterior vaginal wall and holds it vertically in order to prevent it from coming in contact with the surrounding tissues and to prevent any drip. The vagina is then cut close around the cervix. An open sponge is then introduced into the vagina with long forceps. Additional Allis forceps are placed on the cut vagina anteriorly, laterally, and posteriorly in order to maintain the vaginal cuff vertically and on stretch (Fig. 2). The vagina is then closed and the sponges from the cul-de-sac are removed. All instruments are discarded. The vaginal fascia is then sewed; the uterine vessels, the round and the infundibulopelvic ligaments

*Read at a meeting of the Philadelphia Obstetrical Society, Jan. 4, 1945.

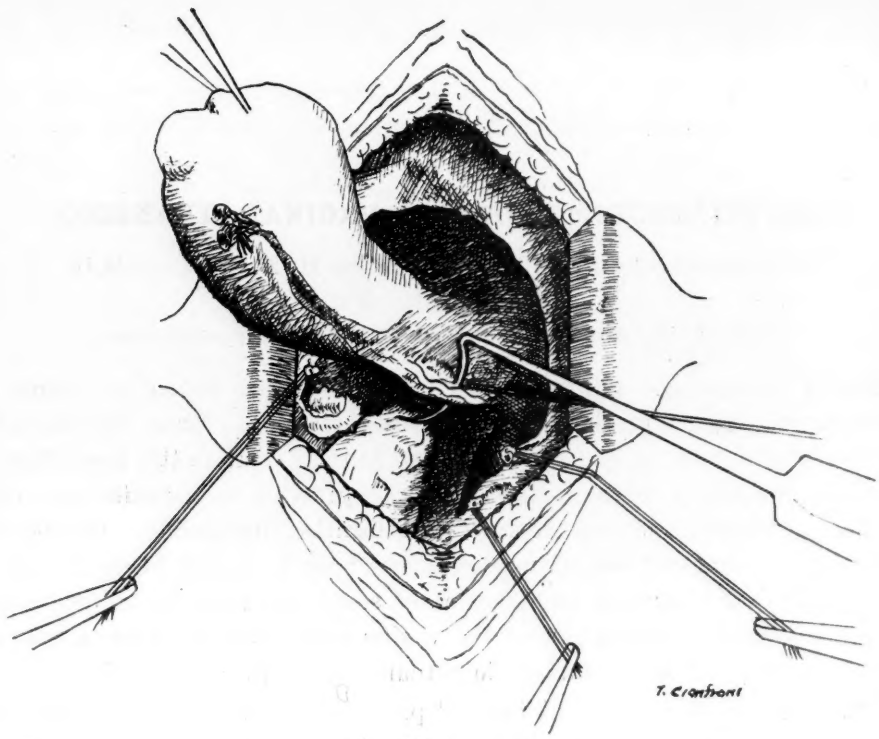

Fig. 1.—Showing the doubly threaded ligature carrier passed at right angles to the long axis of the uterus, and close to the cervix, to avoid the ureters.

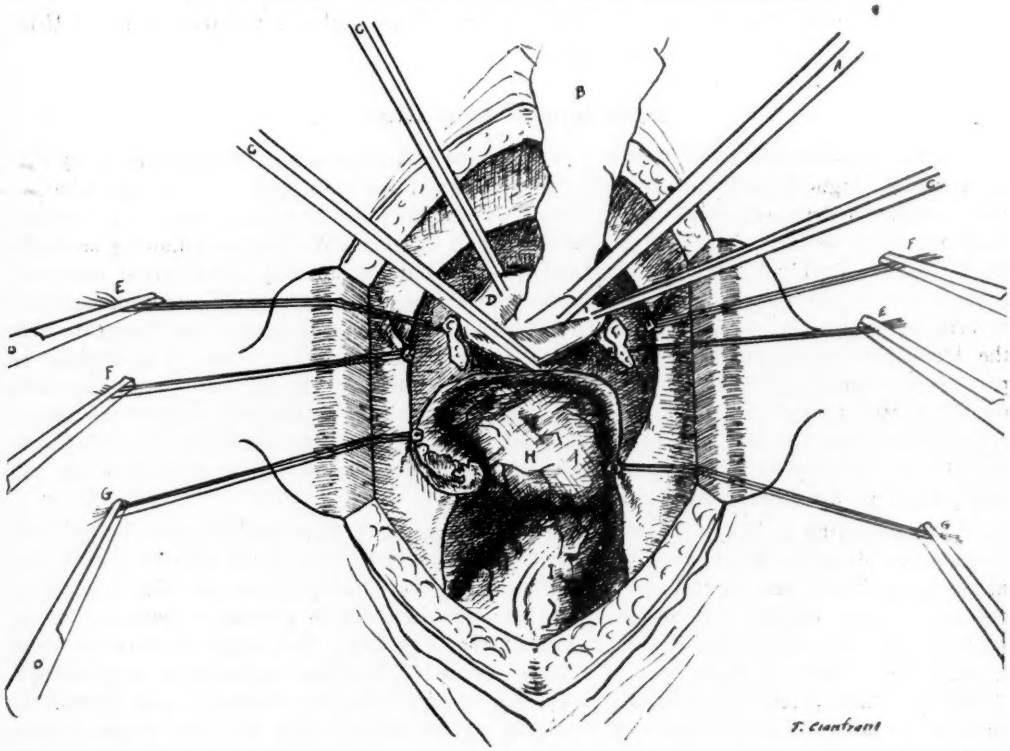

Fig. 2.—*A*, Long forceps; *B*, sponge; *C*, Allis forceps; *D*, vaginal cuff; *E*, ligature on the uterine vessels; *F*, ligature on the round ligament; *G*, ligature on the infundibulopelvic ligament; *H*, sponges in the cul-de-sac; *I*, rectum.

Allis forceps are placed on the vaginal cuff in order to maintain it vertically and on stretch. An open sponge is then introduced into the vagina with long forceps.

are retied; and the closure of the broad ligament is started at one infundibulopelvic ligament and continued to the one on the opposite side with a running suture. Neither abdominal nor pelvic drainage is used.

We are not including in this series the numerous cases of supravaginal hysterectomy with complete coning of the cervix done in this clinic. In these the technique of vaginal isolation, instead of attempts at sterilization, was used, and no peritonitis developed in any of them postoperatively.

Review of Cases

A thorough study of the charts of the 130 cases was made to ascertain facts that were pertinent to the operative results, and only these were recorded. The series consisted of 94 Negroes and 34 whites; 85 per cent were in the age group of 30 to 45 years; 53 of the cases had appendectomies done; and 27 had positive Wassermanns.

TABLE I. PATHOLOGIC CONDITIONS ENCOUNTERED

65	fibroids
23	fibroids and pyosalpinx
24	bilateral pyosalpinx
1	fibroid with endometriosis
4	fibroids with adenomyosis
3	fibroids with fundal cancer
2	fibroids with dermoid
1	granulosa-cell tumor of ovary
1	Krukenberg tumor of the ovary
4	ovarian cysts
1	bilateral solid carcinoma of ovaries
1	cyst of ovary with adhesions
130	

It is to be noted that the cases included in this report were generally of a very serious nature, since most of our ward work is done on neglected cases, due to the social stratum from which these patients come.

TABLE II. TEMPERATURE ANALYSIS

GROUP	NO. OF CASES	DAY OF NORMAL TEMPERATURE	HIGHEST TEMPERATURE	DAY OF HIGHEST TEMPERATURE
A	101	5th	100.2° F. (99.2-102° F.)	2nd
B	14	8th	101.5° F. (101-104° F.)	5th
C	15	10th	102.8° F. (101-103° F.)	13th

We divided the cases into three groups, the figures used are the mean, calculated from the low and high of each group.

Group A.—Cases that had normal temperatures within the first week. There were 101 such cases; they had a normal temperature by the fifth day with the highest temperature of 100.2° F. on the second day.

Group B.—Cases that had fever for more than one week. There were 14 of these cases; they had a normal temperature by the eighth day, with the highest temperature of 101.5° F. on the fifth day.

Group C.—These were the cases with demonstrable complications. There were 15 cases; they had a normal temperature by the tenth day with the highest temperature of 102.8° F. by the thirteenth day. This is the only group that required extra hospitalization, being discharged on the twenty-fourth day on an average, instead of the usual sixteen to seventeen days.

TABLE III. COMPLICATIONS

6	severe wound infections
3	moderate wound infections
3	indurated broad ligaments
1	thrombophlebitis of the leg
1	pyelitis
1	cystitis
15	

We do not believe that appendectomies increased the operative risk in this series because, of the 15 cases with complications, only 6 had appendectomies, which is less than 50 per cent. The 115 cases with no complications contained 47 appendectomies, which is approximately the same proportion as found in the 15 cases with complications.

Positive Wassermanns did not affect the postoperative course in this series. There were many more negative than positive Wassermanns in the group with complications. Of the 27 positive Wassermanns in the entire series, only 3 occurred in the group of 15 cases with complications.

The presence of pelvic inflammatory disease may have had some influence on the postoperative course of our cases, because there were 8 cases of pelvic inflammatory disease in the 15 cases of complications, whereas there were only 39 cases of pelvic inflammatory disease in the 115 cases without actual complications. Included in these 115 cases are the 14 cases with a protracted fever for more than one week, but with no demonstrable complications; they showed the same proportion, namely, 5 cases of pelvic inflammatory disease in 14 cases.

Mortality.—There were two deaths, both from pulmonary embolism.

1. One occurred in a Negro women, 38 years old, with bilateral intraligamentary fibroids. Her postoperative convalescence was uneventful until the fourteenth day, when she developed a pulmonary embolism and died. The autopsy showed a hemorrhagic infarct of the right lung, and acute pulmonary embolism, and thrombosis and embolism of the right internal iliac veins.

2. The second was in a white woman, 47 years old, with multinodular fibroids. Her postoperative convalescence was uneventful; she was out of bed on the fourteenth day. On the sixteenth day, before going home, she developed a pulmonary embolism and died. An autopsy was not obtained.

Discussion

The results in this series approximates other studies of panhysterectomies *with* vaginal sterilization. Most of the cases reported had diseased cervices, and in this clinic a diseased cervix in a case that needs a hysterectomy always demands removal, except in some cases in which removal increases the operative risk. In these instances we must be content with a supravaginal hysterectomy with partial coning followed by cauterization at some future time, or hysterectomy with complete coning of the cervix. Unless the patient's condition militates against it, panhysterectomy is preferred even in cases with apparently normal cervices. Our technique, in which we do not use clamps but instead cut around the vagina close to the cervix, minimizes the danger of a short vagina. Also, in patients in whom hysterectomy has been preceded by extensive plastics in which ligaments have been much disturbed, panhysterectomy may not be the procedure of choice. This preference for panhysterectomy instead of supravaginal operation in cases with apparently healthy cervices is the result of repeated findings of cervical cysts deep and high up, noticed when cutting across the cervix in a supravaginal operation. These deep-seated cysts, and the at-

tendant infection that is nearly always present, are difficult to eradicate by the subsequent cauterization or electrocoagulation. Most important of all is the threat of cervical carcinoma, which always remains unless a panhysterectomy has been done, and we wish to emphasize that this is a real threat to the patient's future welfare, despite the fact that only three of our cases of supravaginal hysterectomies have returned to us with stump carcinoma; but we feel sure that a certain number of them have found, or will at some time find their way to some other clinic for this condition.

Because we believe the use of soap and water and the application of antiseptics vaginally prior to or at the time of operation will not sterilize the vagina, we have emphasized the technique which prevents peritoneal contamination rather than vaginal sterilization. We further believe from long experience that the sponge which is introduced into the vagina from above at operation, together with placing two sponges in the cul-de-sac, and the maintaining of the vaginal cuff vertically on stretch, is sufficient to prevent any spilling of vaginal secretions intraperitoneally, as evidenced by lack of postoperative peritonitis.

Summary and Conclusions

1. One hundred and thirty cases of panhysterectomy are reported without preoperative vaginal sterilization.

2. A surgical technique is described to safeguard the peritoneal cavity from contamination.

3. There was no peritonitis or other complication which could be attributed to this technique.

4. A surgeon can therefore proceed with impunity in an unforseen panhysterectomy, even though he has not prepared the vagina, provided the above-described technique is followed.

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CESAREAN SECTION ON A POLIOMYELITIC PATIENT CONFINED TO A RESPIRATOR

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PREGNANCY complicated by acute anterior poliomyelitis with paralysis of the respiratory muscles requiring continuous confinement in a respirator is rare. The number of patients in this group who have respiratory paralysis at term is small because so fulminating a process leads rapidly to death or to improvement before delivery. Aycock[1] reports that the incidence of pregnancy in all poliomyelitis cases is less than 1 in 1,000; and the incidence of poliomyelitis among pregnant women is less than 1 in 50,000. If Brahdy's[2] findings, that 4 per cent of all poliomyelitis patients are respirator cases, may be applied generally, then, hypothetically, less than 1 in 1,000,000 pregnant women would have respiratory poliomyelitis. Of these only a small percentage would still be dependent upon artificial respiration at the time of delivery. During the recent epidemic, in our experience with 423 cases of poliomyelitis, 40 of whom were women in the childbearing age, there were three pregnancies. The apparent discrepancy with Aycock's statistics may be attributed to the greater incidence in older age groups during this epidemic.

Peelen[3] tabulates 29 reported cases of poliomyelitis in pregnancy, adding two of his own, and discusses various aspects of the problem. Gillespie[4] reports a cesarean section in a pregnant woman with respiratory paralysis due to acute poliomyelitis. He unsuccessfully attempted to arrest labor with progesterone and large doses of nembutal, but finally performed a section to procure a live baby, as the mother was considered moribund. The mother improved, but the baby died six hours after birth of intracranial hemorrhage. Spishakoff, Golenternek, and Bower[5] report a premature spontaneous delivery using a resuscitator alternating with the respirator. The mother's condition was so grave that they were prepared for a postmortem cesarean section. The insurmountable difficulty of forceps application and of low spinal or presacral anesthesia are discussed in their paper. Hornung and Creutzfeldt[6] report a section performed three weeks before term upon a pregnant woman with respiratory paralysis. A respirator was not used, and she died forty-eight hours later of respiratory failure. The baby survived.

We disagree entirely with the belief, held by many, that poliomyelitis usually has no adverse influence on pregnancy, and vice versa. As is well known, bladder paralysis with cystitis and ascending infection may lead to pyelonephritis. Impaired bowel function, with constantly recurring fecal impactions and marked distention pressing on a paralyzed diaphragm, may increase the already serious hypoxia. Removal of a patient from a respirator to allow her to learn to breathe spontaneously for gradually increasing intervals is not without danger near term. Many authors have noted the disappearance of cyanosis and thoracic discomfort, and the onset of easier breathing upon emptying the uterus. McGoogan[7] suggests that in some cases of poliomyelitis the added strain of pregnancy may retard complete recovery, but that after delivery, the burden having been removed, regeneration may progress more rapidly. In other instances, he believes, the disease might not have been so

extensive had pregnancy not been present. Poliomyelitis probably has no effect on the fetus in utero, as no authentic intrauterine infections have been reported. If any immunity is imparted to the baby during an attack in the mother, it must be short-lived, as a number of cases of infantile poliomyelitis have been reported under the age of 1 year, a few under 1 month, and one as early as 9 days.[8]

Cushny,[9] in 1906, established the fact that the automatic rhythmic uterine contractions are on a myogenic, rather than a neurogenic basis, and that completion of the first stage of labor is possible after severance of all nerves to the uterus. Transection of the spinal cord, and even extirpation of the sympathetic nerve supply to the uterus, does not alter its inherent contractility. Obstetricians had observed previously that vaginal delivery is possible in women paralyzed by cord tumors and vertebral fractures, with loss of function of the muscles of the abdomen and extremities (Kleinberg and Horwitz[10]).

It is obvious that complete paralysis of all the voluntary forces definitely hinders the progress of the second stage of labor, and that in such cases external help is necessary. In addition, paralysis and overdistention of the bladder and bowel, with constantly reforming fecal impactions, necessitate frequent cathartics and enemas, which accentuate Braxton Hicks' contractions, thus possibly inducing labor prematurely. Bladder paralysis and distention may interfere with the normal third stage contractions and thus increase the possibility of hemorrhage (Miller[11]).

Helms[12] believes that when respiratory paralysis is present during the last weeks of pregnancy, respiration will be facilitated by emptying the uterus, which he considers indicated. Morrow and Luria[13] likewise suggest cesarean section if the increasing size of the uterus hampers respiration. McGoogan[7] aptly states: "... emptying of the uterus should be done if the enlargement of the uterus is sufficient to encroach upon the diaphragm. This should be done ... to improve the patient's lung aeration and to postpone the onset of fatal respiratory paralysis." Peelen[3] is in accord with this view. Lewin[14] says: "Interruption of pregnancy should not be undertaken except in those instances in which the uterus encroaches upon the diaphragm and there is diaphragmatic paralysis; or in case of severe cystitis or other complications." Brahdy and Lenarsky[8] are of the opinion that "uncomplicated poliomyelitis, excluding respiratory paralysis, is not an indication for the interruption of pregnancy." In a personal communication from Kleinberg,[10] he qualifies his published statement, saying that section may be indicated in a respirator patient.

There seems to be an erroneous belief that during the agonal period preceding death, the patient will have a precipitous delivery. This misconception may have resulted in a needlessly high rate of fetal mortality, which might have been avoided by more active measures. Fetal mortality in postmortem cesarean section is very high because futile attempts at maternal resuscitation are usually prolonged unduly.

In our case, the respiratory paralysis was accompanied by the loss of almost all voluntary motor function of spinal innervation, plus facial paralysis as a manifestation of bulbar involvement. The pregnancy was further complicated by breech presentation, pyelonephritis, and acute glomerulonephritis.

Case Report

E. M., a 27-year-old pregnant white housewife, was admitted to the Poliomyelitis Service of the Kingston Avenue Hospital on Aug. 26, 1944, with a two-day history of an ascending type of poliomyelitis; headache, vomiting, nuchal rigidity, weakness of both legs, fourteen-hour urinary retention, and then difficulty in breathing and weakness of the left arm.

Her history included one previous uncomplicated pregnancy which terminated five years ago in spontaneous delivery at term of a 7-pound, 13-ounce normal male child, after a labor of nine hours. An episiotomy was necessary. Her last menstrual period was March 15, 1944, and was normal. The pregnancy was uncomplicated prior to the onset of the present illness.

Examination on admission revealed an acutely ill woman whose voice was faint and skin dusky. She could count only to 2 in one breath. Her temperature was 101° F., pulse 100, and respirations 28. Her lungs were poorly ventilated. The abdomen was enlarged by a five-months' pregnancy and a markedly distended bladder. There was rigidity of the neck and back, and bilateral weakness of the iliopsoas, ham-strings, triceps, biceps, intercostals, diaphragm, and of the left deltoid. There was also slight left lower facial palsy. Deep tendon and abdominal reflexes were absent. The Kernig sign was positive bilaterally. Other findings were noncontributory. The spinal fluid was under increased pressure, slightly cloudy, sterile, and contained 520 cells per cubic millimeter, 70 per cent lymphocytes and 30 per cent polynuclears. Glucose was 66 and total protein 90 mg. per cent.

Upon admission, the patient was placed in a respirator. Her temperature became normal on the second hospital day, and it was then noted that the patient had no visible respiratory excursion when removed from the respirator, and turned cyanotic in a few seconds. Paralysis had extended to the right upper limb. Bearing down, coughing, and defecation were impossible. There was marked muscular pain in the extremities, chest, and shoulders, intensified by passive motion and pressure, as well as severe lower lumbar and right sacroiliac pain.

Painful intermittent uterine contractions appeared and became progressively more frequent and severe. They were often provoked by the cleansing enemas, which were necessary every other day despite the use of large doses of bland cathartics, oil enemas, and frequent digital removal of fecal impactions. External pelvic measurements were ample. Active fetal movements were present until delivery, but auscultation of the fetal heart was impossible because of the noise of the respirator. Frequent catheterization was necessary until the ninth day, when she developed paradoxical incontinence with a residual of 450 c.c. The urine specimens showed a trace of albumin and rare red and white blood cells. Culture was positive for *B. coli*. Mercurochrome was instilled into the bladder every second day in the hope of preventing ascending infection.

On the twentieth day, she developed acute right-sided pyelitis with large amounts of *B. coli* in the urine. On the sixty-eighth day, a superimposed acute diffuse glomerulonephritis appeared, and became progressively worse.

At no time was edema evident. On the seventy-seventh day the patient vomited persistently for twenty-four hours, returning food eaten more than twelve hours previously. She had almost continuous uterine contractions during that day. Vaginal examination revealed a thick, long, closed cervix. The patient had been confined to a respirator continuously for ten weeks, and as the pregnancy advanced both the rate and pressure had to be increased to compensate for the greater resistance to diaphragmatic motion.

Considering the nephropathy and the fact that the fetus was in breech presentation, it was deemed advisable to take advantage of a slight improvement in the patient's general condition to do a cesarean section at the thirty-fifth week of gestation, eighty-two days after admission. Consultations confirmed our decision, lest by delay we permit further kidney damage and perhaps intrauterine fetal death. A third transfusion of 500 c.c. of whole blood was given. Because the respirator could not be moved to the main operating room, an emergency operating room was improvised. An endotracheal tube was passed. The patient was removed from the respirator and maintained with a resuscitator until anesthesia was begun. Under cyclopropane insufflation anesthesia, with manual positive pressure to a rebreathing bag, a classical cesarean section through the placental site was done. A healthy 4-pound, 5-ounce premature female child was extracted by the breech in three and a half minutes, crying and breathing spontaneously. Placenta and membranes were removed manually. The uterus contracted well after pituitrin and was closed in layers. The abdomen was closed by our usual technique.

The entire time from incision to closure was twenty-five minutes. When the operation was completed, the Kreiselman apparatus was again used until the patient was returned to the respirator. The sutures were cut on the seventh postoperative day and removed on the ninth, with healing per primam.

The baby was given routine neonatal care and was transferred to a premature unit at the Kings County Hospital. Her course was uncomplicated and, at four months, she weighed 9 pounds.

The facilitation of chest expansion detected by the anesthetist upon removal of the baby was noted by the patient as she recovered from the anesthesia, and she was more comfortable thereafter, even at a reduced respirator pressure. The patient voided spontaneously five hours after the operation. Her oral temperature rose to 100.4° F. eleven hours postoperatively, but subsided promptly. Gaseous distention was absent throughout. Prostigmine and a rectal tube were employed prophylactically.

The breasts continued to secrete in spite of early and prolonged use of stilbestrol, supplemented later by testosterone. The patient could not tolerate a breast binder because it restricted the full chest expansion produced by the respirator.

Both forearms have a limited range of feeble motion, and the hands can be used effectively. The lower limbs can manifest feeble mass movements. The slight left facial paralysis remains unchanged.

The blood chemistries and the urine returned to normal within a month after the operation, except that urine cultures are still positive. In spite of 500,000 units of penicillin, a prolonged course of sulfadiazine, and the protracted use of ammonium mandelate and ammonium chloride, the urine has not been sterilized. The red blood count has risen to 4,350,000 and the hemoglobin 81 per cent. The blood pressure has fallen and varies between 110/60 and 140/100.

Comment.—The care of a patient confined to a respirator is limited by the difficulty of manipulation. Since the patient was entirely dependent upon the respirator, we were cautious not to remove her from the apparatus for more than two minutes at a time, to avoid fetal anoxia. Only after delivery was any attempt made to determine how long the patient could remain out of the respirator.

The generalized muscular pains due to the extensive poliomyelitic involvement and the costovertebral pain associated with the kidney infection, prevented change of position and other manipulation. The gravid uterus contributed to the respiratory embarrassment and to the ascending urinary infection. The patient was constantly wet because of urinary incontinence and perspiration, aggravated by the summer heat. One of us (S. S. B.), in order to reduce the humidity of the air within the respirator and thus facilitate the evaporation of perspiration, introduced anhydrous calcium chloride as a desiccating agent. We feel that this contributed greatly to the patient's comfort and minimized moisture as a factor in the formation of bedsores. Pressure and stasis could not be relieved because passive motion produced most agonizing pain.

On admission, as the prognosis was doubtful, provision was made for postmortem cesarean section. However, the patient's condition remained static and the problem of ultimate delivery confronted us. Consultation with specialists in obstetrics and anesthiology suggested the following methods of delivery: (1) spontaneous delivery, (2) delivery after full dilatation of the cervix assisted by low forceps or pituitrin, (3) abdominal cesarean section, classical or low double flap.

Vaginal delivery within the respirator is possible, but offers little opportunity for control and asepsis because of the size of the chamber and the spacing of its portholes.

The respirator[15, 16] consists of a huge airtight cylindrical chamber enclosing the patient's body with the head protruding through a rubber collar. A bellows or a diaphragm operated by an electric motor produces rhythmic changes of pressure. The chamber has several portholes. Breech extraction, forceps to the aftercoming head, episiotomy, manual removal of the placenta, repair of a lacerated cervix or perineum, and control of postpartum hemorrhage are impossible. Delivery within a respirator is further contraindicated by the danger to which a newborn infant is subjected, being unable to synchronize with a respirator set at an adult rate and pressure. Moreover, the changes in atmospheric pressure within the respirator, equivalent to sudden ascent and descent from an altitude of about 1,300 feet, might cause pulmonary or intracranial hemorrhage or air embolism. Other means of artificial respiration during labor might have overcome some of these objections and permitted vaginal delivery. However, the fetus being in a breech presentation, and faced with the threat of prematurity, the pressure of uterine contractions on its head would not be insignificant. A possibly rapid extraction through an unprepared genital passage would be hazardous. We also felt that a patient unable to cough, defecate, or breathe because of broken reflex arcs, is sufficiently handicapped to be spared the added strain of labor.

The classical section was selected as the fastest and simplest method, and the various means of anesthesia and resuscitation at our disposal were then studied. The anesthestic aspect is discussed at length in a companion paper.[17] Cyclopropane was chosen as the safest and most flexible agent, allowing one anesthetist to control both aeration and anesthesia.

An experimental head respirator designed by J. H. Emerson for use in this case was abandoned because it precluded the use of inhalation anesthesia. The chest respirator could not be used because of the time required to apply it even to a normal, cooperative subject, and because it would have interfered with abdominal surgery. The plan to build a special respirator room similar to the one in Boston was given up after consultation with naval experts because the effect of the constantly changing pressure was feared.

Positive pressure, using a face mask, at first with a rebreathing bag and later with the Kreiselman[18] resuscitator, was employed frequently both to accustom the patient to its use and to facilitate examination, treatment, and nursing care. Manual compression of the rubber bag distends the lungs, and when properly performed provides good aeration at no hazard. An automatic modification, the E & J resuscitator, caused discomfort and apprehension in our patient. Gaseous anesthesia cannot be given with this machine, nor with the Kreiselman resuscitator, which furnishes oxygen through a face mask at an adjustable pressure that is both safe and adequate. The rate and rhythm are under the control of the operator, and can be made to supplement any voluntary respiratory efforts of the patient, while most other devices may oppose them. Our patient did well on the rebreathing bag, but fatigue of the operator led to irregularities in the rhythm and depth, which in turn made the patient fearful

and uncooperative. She was, on the other hand, relaxed and confident when the Kreiselman apparatus was used, and had smooth and even oxygenation at all times. She was therefore maintained with this resuscitator in transit between the respirator and the operating table, and until anesthesia was begun. Fully satisfactory anesthesia was given under positive pressure from the rebreathing bag, after passage of an endotracheal catheter under direct visualization. The new Kreiselman bellows[19] resuscitator, which is manually operated and can deliver gaseous anesthesia and oxygen, was an alternative means.

We believe that the action of the respirator played a large part in preventing distention, whether by a milking action or by preventing splinting of the abdomen, and helped prevent pulmonary complications by forcing full chest expansion. Though we had feared that delayed healing would follow from the constant abdominal motion caused by the respirator, we were favorably surprised. Prolonged uncontrollable lactation was the only possible untoward effect of the respirator, which simulated a large breast pump.

Summary and Conclusions

A case of pregnancy complicated by acute anterior poliomyelitis appearing in the fifth month and necessitating the continuous use of a respirator has been presented.

We believe that a patient with a quadriplegia plus almost total paralysis of all the muscles below the clavicles should be spared the added strain of labor. The pregnancy was further complicated by acute pyelonephritis and acute diffuse glomerulonephritis. The progression of this nephropathy and the possibility of intrauterine fetal death required prompt action.

The patient was removed from the respirator and maintained with positive pressure resuscitation and insufflation anesthesia with cyclopropane, while a classical cesarean section was performed. A healthy premature baby was delivered at the thirty-fifth week of gestation, followed by improvement in the condition of the mother. The subsequent course of events confirms our decision that an elective cesarean section was the best procedure under the circumstances.

The rationale of treatment is given, with discussion of means of anesthesia and resuscitation. The use of anhydrous calcium chloride is recommended to increase the comfort of respirator patients. The method presented is believed by us applicable to all respirator cases requiring laparotomy.

Addendum

Follow-up.—The authors regret to report that the patient succumbed on July 14, 1945. Her urinary infection persisted and, five months post partum, stones were first observed. Subsequently, a left perinephritic abscess developed which required incision and drainage. Three months postpartum, the patient developed a massive atelectasis with almost complete shifting of the heart and mediastinum into the right chest. Bronchoscopic suction gave only temporary relief. These complications resulted in the patient's death 322 days after admission and 242 days after laparotomy.

We are greatly indebted to Drs. E. A. Rovenstine of New York City and Joseph Kreiselman of Washington, D. C., for the able handling of the anesthesia, without which we could not have succeeded. We also thank Drs. A. C. Beck, Harvey B. Matthews, and Morris Glass of the Long Island College of Medicine and Dr. H. J. Stander of the Cornell University College of Medicine for their consultation, and Dr. Nathan Reibstein for his technical assistance, as well as our many other colleagues who advised us by mail. We are grateful, too, to Dr. E. M. Bernecker, Commissioner of Hospitals, who placed all necessary facilities at our disposal, without which this mother and baby could not have survived.

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DOUBLE UTERUS AND DOUBLE VAGINA

Identical Doubles Demonstrated by Colpohysterosalpingography

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TAYLOR[1] wisely advocated simplification and uniformity of nomenclature relating to organic variants which are the result of lack of fusion of the Müllerian ducts and/or irregularities of canalization. With his position we are heartily in accord. This author cited DeLee as listing nine variations and Graves eight types which do not correspond. He further declared that the many terms do not give a word picture, but require a detailed description. His simplified classification follows:

1. Uterus arcuatus.
2. Double uterus with a single cervix.
3. Septate uterus with a single or a septate vagina.
4. Double uterus with a double cervix.
5. Uterus with a rudimentary horn or absence of one horn.

It is not our intention to discuss extensively here these embryologic phenomena, but simply to reiterate the well-known fact that these variants from normal are due to irregularities of fusion in the juncture of the Müllerian ducts, which normally form the symmetrical halves of the corpus uteri. These abnormalities may also be associated with irregularities in canalization in the development of the urogenital sinus or lower uterine and vaginal tract.

Frequency of Occurrence

As estimated by Taylor,[1] the deformity occurs once in about 1,500 obstetric cases and once in about 2,000 gynecologic cases. He thought that even the specialist may see but a few cases in a lifetime. Ewer[2] was of the opinion that abnormalities of the female generative tract are more frequent than one is prone to believe, and cited Falls, who noted the presence of uterus arcuatus in 3.8 per cent of 7,553 obstetric cases. Moore[3] also believed the incidence of this abnormality is much higher than the imperfect records would indicate and from private records drew the conclusion that "one in five or six hundred women present some definite congenital deflexion from gestation slips in the embryological assembly line." He also thought many women go through life without awareness of the abnormality or at least without disclosing the condition. This author further observed that this anomaly is frequently associated with abnormalities of the genitourinary system and mentioned several cases on record in which pregnancy of both uteri occurred concurrently with safe outcome to both babies and the mother. Conversely, Obenour,[4] in 1942, searched the literature published since 1879, but could find no record of roentgenograms or of actual photographs of double uterus and vagina.

Practical Considerations

Schauffler[5] quoted the record of a case which included the more incorrect than correct diagnoses made by nine physicians, and also this comment regarding the patient, "She was unnecessarily pounded, thumped, curetted, aborted, and laparotomized, mainly because of a complete double uterus which presented diagnostic difficulties during pregnancy." He also observed that this functional variant is a definite asset to marital relations and inferred that fertility and the sex urge are distributed among women with this abnormality in the same generous proportions as their organic equipment. He reported seeing eleven patients in six years with duplex anomalies of the urogenital tract. Each had one or more pregnancies, and there was a total of thirty-two.

Ewer[2] cited Findley, who in 1926 analyzed 135 cases of uterus didelphys with septate vagina reported in the literature. The patients in these cases gave birth to 216 full-term babies, including 13 sets of twins; 83 were delivered spontaneously, and 23 by cesarean section; 13 presented by breech. Fifteen were born prematurely, and there were 86 abortions. This author then sagely observed that Nature is resourceful and noted the corollary seen in many mammals thus normally equipped. He added that if this is only an expression of atavism, "it is perhaps surprising that trouble is not more often encountered."

Diagnosis

Helpful diagnostic signs in this condition are, according to Schauffler,[5] "irregular menses, dyspareunia, repeated unexplained abortions or miscarriage, and repeated malposition of fetus." Uterosalpingograms, he stated, yield the most complete information available. All writers agree that pseudomenstruation from the nonpregnant side occurs commonly and may be a sign of threatened abortion because the decidua is under a different endocrine influence. Passage of a decidual cast should always be investigated, though it is not necessarily indicative of threatened abortion. Schauffler[5] advised general and special prenatal care, and measures to strengthen and protect the ovular attachment.

There is general agreement that the nonpregnant horn rotating posteriorly and altering the birth canal is a common complication. Awareness of this anomaly at delivery calls for ready operative equipment for complications involving the vagina and cervix. Taylor[1] declared that "incarceration of the nonpregnant uterus with a breech presentation at term is an absolute indication for delivery by cesarean section." Post partum, likewise, there may be adherent placenta, postpartum hemorrhage, faulty involution, and other irregularities. We believe that roentgen pelvimetry should be added routinely to the armamentarium of the diagnostician.

Report of Case

Mrs. C. E. B., a white woman aged 24 years, first came under our observation on Sept. 10, 1944. The reason for consulting a physician at this time was nervousness, pain in the lower part of the abdomen aggravated by intercourse, irregular menses, and severe cramps with menses, causing her to remain in bed for from one to three days during each menstrual

period. Sterility was also a prominent complaint. Although she had in the past years consulted ten physicians, none had ever advised her of her abnormal condition.

She had had the usual diseases of childhood. Menses had begun at the age of 15 years and had always been irregular and painful. First married at the age of 18 years, she had after eleven months been divorced. She had been married since she was 22 years of age to her present husband. She had never experienced any sense of gratification in the sexual act and had never been pregnant. Following an acute attack of appendicitis five years previously, an appendectomy had been performed. There was no history of venereal disease.

The patient was 66 inches in height and weighed 158 pounds. The blood pressure, taken on several consecutive occasions, averaged 125/75. Urinalysis of a catheterized specimen gave negative results. On two occasions the reaction to the Kahn test was negative.

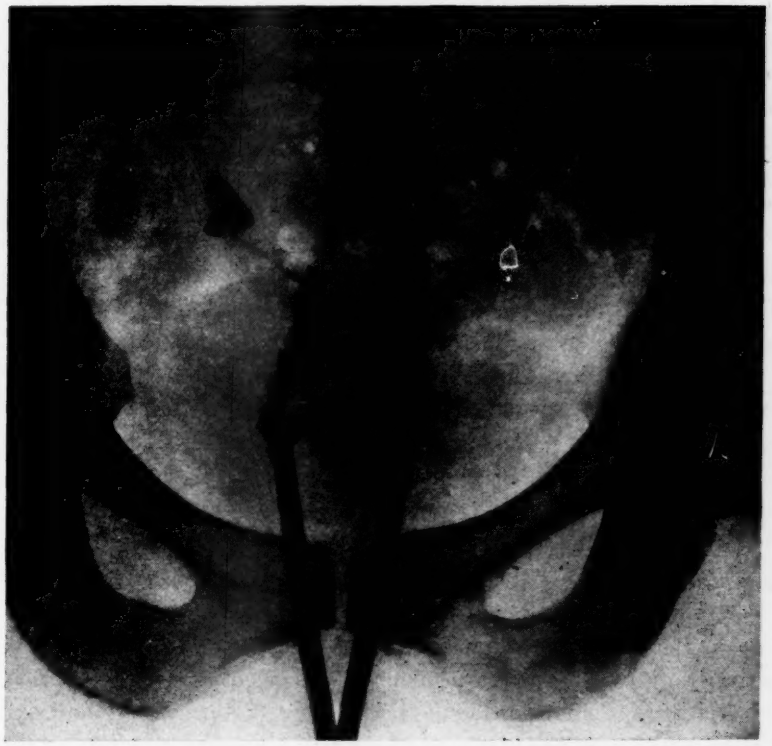

Fig. 1.—Following injection of iodochlorol into the cervices through a catheter, two cervices, two cervical canals, two separate uteri, and two tubes are clearly outlined in this roentgenogram. The tube on the right side is partially filled with oil and air; the tube on the left side is well filled with the opaque oil.

On examination of the genital tract, it was noted that a complete septum was present in the vagina extending down to within ½ inch of the external orifice. Two distinct cervices were palpated, with the septum extending in the vagina up to and forming a complete vaginal wall to the separate cervices.

The patient returned for examination at the first menstrual period, which began three days after the first visit. The menstrual flow was demonstrated coming equally from the separate cervices.

The roentgenologic report from here on proved most conclusive. A small catheter was introduced into the uterine canal on each side and injected with about 5 c.c. of iodochlorol. As shown in Fig. 1, the roentgenogram then taken plainly demonstrates only one tube to each of the separate uteri. These tubes are patulous and appear normal. The two cervices, two

cervical canals, and two separate uteri are also clearly outlined. Roentgen study of the urinary tract showed, on intravenous injection of neo-iopax, no evidence of reduplication of the kidneys or ureters. In addition, roentgen examination of the chest gave entirely negative results, and the results of roentgen pelvimetry were also normal.

Summary

Simple and uniform nomenclature for describing abnormalities of the female genital tract is advocated. It is suggested that these anomalies occur more frequently than is generally believed. Diagnostic signs are reviewed, and routine roentgen pelvimetry as an aid in diagnosis is advised.

A case is reported in which a double uterus and a double vagina were demonstrated roentgenologically.

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THE SUBPERITONEAL BALDY-WEBSTER UTERINE SUSPENSION*

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SINCE Olshausen performed the first modern suspension of the uterus, many techniques have been devised, practiced, and discarded. Because of the principles embodied in the Baldy-Webster type of uterine suspension, this procedure has been able to enjoy wide popularity and use among gynecologists for many years. The utilization of the proximal end of the round ligament to support and elevate the prolapsed ovary, together with the fact that the uterus remains a mobile pelvic viscus not attached in any way to the abdominal wall, are the main factors responsible for the success of the operation. It has been demonstrated repeatedly that this procedure causes no complication in subsequent pregnancy and holds up well following delivery.

There are, however, several points of weakness in the procedure. The first disadvantage is the necessity of perforating the broad ligament in order to draw a loop of the round ligament through it. This has resulted in intestinal obstruction. Since Richardson[2] reported the first such complication, following the Baldy-Webster procedure in 1920, ten other cases have been added to the English literature.[3-9] This serious complication, sometimes developing years after the performance of the operation, was due in every case to the incarceration of a knuckle of bowel into the opening in the broad ligament which had become enlarged by the traction of the uterus during the years.

The second disadvantage lies in the presence of the joined and uncovered loops of round ligament on the posterior surface of the uterus. This area with its knots of suture material offers a congenial site for the development of intestinal adhesions with their many potential sequelae. Such a case was observed in which the bowel was adhered to this area on the back of the uterus causing partial intestinal obstruction and necessitating a second laparotomy two weeks after the first. Another disadvantage is the possibility of failure of the suspension because of the lack of union between the serosa of the round ligament and the serosa of the uterus at the small area of suture contact between the two.

With the idea of avoiding these disadvantages, one of us (E. A. S.) in 1942, devised a subperitoneal approach which accomplished the identical results of the Baldy-Webster procedure without its drawbacks. The operation is performed as follows:

Method

After anesthesia and proper preparation, the lower abdomen is incised in the midline as for any intrapelvic procedure. The retroverted uterus is elevated and held in anteposition. A vertical incision, ¾ to 1 inch long, is made on the posterior uterine wall, its upper end corresponding to the intertubal line (Fig. 1). This incision is very superficial, only the peritoneal covering of the uterus being divided.

*Presented at a meeting of the Philadelphia Obstetrical Society, Feb. 1, 1945.

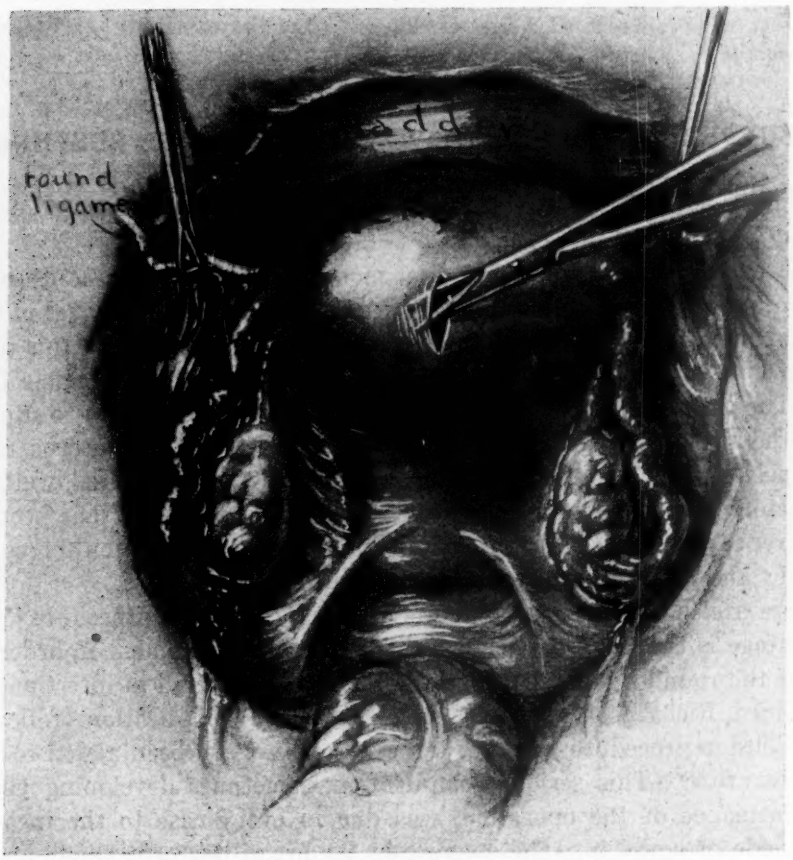

Fig. 1.

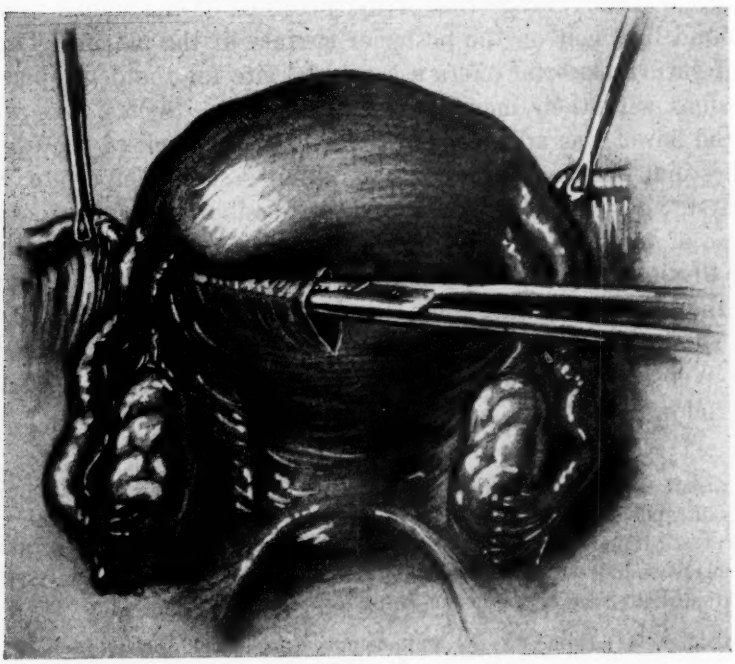

Fig. 2.

With a slender pair of Mayo scissors, a subperitoneal tunnel is made in the posterior uterine wall extending to the insertion of the broad ligament on either side. A slender long-nosed curved hemostat is then introduced into the tunnels on either side and the anterior leaflet of the broad ligament is pierced (Fig. 2). The round ligament is then grasped in the hemostat at the point of its greatest mobility and the loop of ligament drawn back through the tunnel until it appears at the uterine incision (Fig. 3, *A*). This being accomplished on both sides, the loops are approximated with one or two sutures of fine silk, linen or catgut depending upon the preference of the surgeon (Fig. 3, *B*). The vertical incision in the uterine peritoneum is then meticulously closed with very fine catgut and the operation is complete (Fig. 3, *C*).

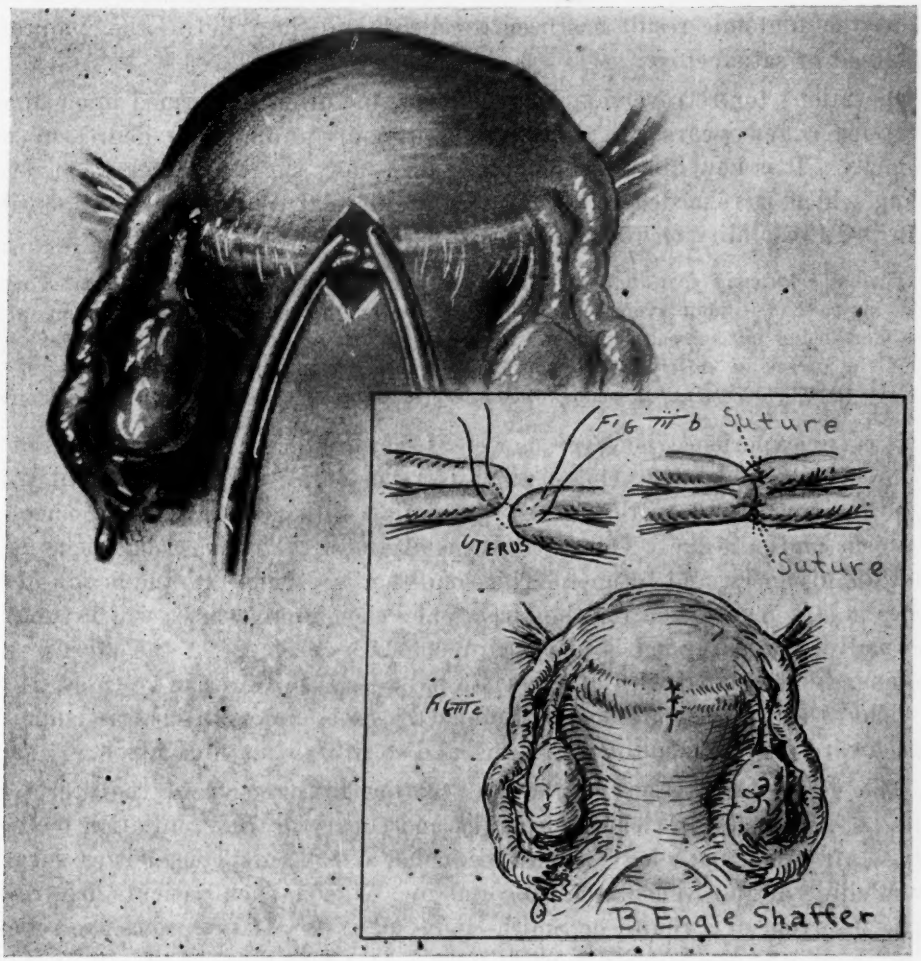

Fig. 3.

It will be noted that the posterior leaflet of the broad ligament is not perforated, so that no opening exists through which the bowel might herniate, nor are there the exposed loops of round ligament on the posterior surface of the uterus. There is much less chance of the suspension breaking down because agglutination between the uterus and round ligaments takes place in two long, buried, and scarified tunnels.

The mechanical principles involved in the original Baldy-Webster operation have not been modified in any way. The uterosacral ligaments may be sutured together when they are greatly relaxed. We have not found it necessary to advance the bladder as proposed by Curtis.

After this method had been practiced for about a year, a search of the literature disclosed the fact that Lagerson[10] of Minneapolis had reported an almost exactly similar operation in 1931. However, Lagerson's paper did not excite much attention and was wholly unknown to us. Because of this and the fact that the gynecologists over the country are not familiar with this valuable technique, we have been prompted to give this report, it being understood that priority for the operation clearly belongs to Lagerson.

There have been thirty-two cases in which the above plan has been followed, with no complications up to this time, and with no known disadvantages. In all of them the anatomic result has been excellent, and the relief of the symptoms complained of satisfactory.

Operations for retroversion of the uterus, too often performed upon flimsy indications a few years ago, have fallen into an unfortunate degree of unpopularity. It is now quite fashionable to decry any surgical attack upon retroversion, which is regarded by some as a nonsurgical condition not responsible for any real disability on the part of the patient.

Theilhaber[11] many years ago first called attention to the fact that uncomplicated retroversion may occur without symptoms. It is well known that congenital retroversion, which is far from being uncommon, seldom causes symptoms. It is also true that the normal position of the uterus in elderly women is that of partial retroversion, and that some of the secondary retrodisplacements in young women, especially after childbirth, cause no symptoms.

It is our experience, however, as well as that of others,[12] that symptoms often postdate the secondary development of retroversion, as the unnatural position causes an impediment to the return circulation with resultant engorgement of the uterus and adnexae. These symptoms are most often sacral backache, menstrual disturbances, and fatigue. This condition is a menace to the health of the ovaries and is responsible for the large, pale, edematous ovaries which function abnormally. Retroversion is often a precursor to prolapse of the uterus[13] and is commonly associated with other pelvic pathology; in Gardner's[14] cases, 94 per cent had other pelvic pathology. Endometriosis is almost always accompanied by backward displacement of the uterus, and sterility is not uncommon.

The gynecologist, therefore, when treating retroversion of the uterus, assumes a responsibility which demands most careful differentiation between cases. All other pathology should be ruled out before considering surgery. In the clinic at the Kensington Hospital for Women, such patients are treated by the insertion of a Smith or Smith-Hodge pessary. If symptoms are relieved for three months, the pessary is withdrawn. In a definite proportion of patients the tone of the supporting structure has been restored, the organ remains in normal anteposition, and the disability disappears. In other patients the uterus shortly becomes retroverted again and the symptoms recur. It is in this group that permanent support seems indicated and in which a surgical suspension brings relief.

Conclusions

1. The Baldy-Webster suspension operation is discussed as to its advantages and disadvantages.

2. The subperitoneal approach is described which avoids the weaknesses of the old Baldy-Webster technique.

3. Retrodisplacement of the uterus is discussed as to symptomatology, cause, and treatment.

1814 SPRUCE STREET

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APLASTIC ANEMIA SIMULATING ECTOPIC GESTATION

Report of a Case

S. KOLODNY, M.D., AND S. T. DELEE, M.D., CHICAGO, ILL.

(From the Obstetrical Department of Cook County Hospital)

ECTOPIC gestation is said to occur once in 200 pregnancies.[1] It is one of the most frequently misdiagnosed acute surgical conditions of the abdomen, so that even in good hands one in four cases is missed. The chief reasons are the atypical history and inconsistent findings. Hence, ectopic pregnancy is justly called the "lues of the abdomen."

It is not the purpose of this report to discuss the differential diagnosis of ectopic pregnancy; however, in reviews of this subject, aplastic anemia is not mentioned nor were we able to discover in the literature a case similar to ours. That this report may have added significance and also by way of interest, a brief discussion of aplastic anemia is presented.

Aplastic anemia was first reported by Ehrlich in 1888.[2] In 1919, Smith[3] reported 64 cases. Its etiology is unknown; however, an unidentified toxin is believed to act upon bone marrow, impeding its activity and causing atrophy. Certain chemical and physical agents have been mentioned, namely, benzol, coal-tar derivatives, gold salts, as well as salts of many metals such as arsenic. Mustard gas, x-rays, and radium have also been suggested. Following septic conditions, such as typhoid and diphtheria, patients have developed aplastic anemia. Parasitic infections, such as ankylostoma, may be a factor. In terminal cases of pernicious anemia and hemolytic anemia, the bone marrow may present the picture of aplastic anemia. Lescher and Hubble[4] believe the disease occurs more often in females, especially between the ages of 15 to 30 years; however, in Thompson, Richter, and Edsall's[5] report of thirteen cases, twelve occurred in males. The youngest patient was 25, the oldest 70, and the average age was 46 years. There is no suggestion of a familial tendency.

The onset is usually insidious, with weakness and a progressive pallor. There may be petechiae or purpuric manifestations. Hemorrhages may occur in the skin, mucous membranes, or any organ of the body, but this is usually a late manifestation. Fever is frequently present. Usually there is no undue loss of weight. On physical examination, there is extreme pallor of the skin, without a lemon-yellow tinge. The heart may be dilated and there may be a systolic murmur on the basis of an anemia. The liver, spleen, and lymph nodes may or may not be enlarged.

The blood picture usually shows erythrocytes 1,000,000 to 1,500,000, hemoglobin about 20 per cent, color index less than one, a leucopenia with about 1,500 leucocytes, platelets usually below 50,000, and an accelerated sedimentation rate. Bleeding time is usually not increased, but clotting time is delayed and there is poor retraction of the clot. The reticulocytes are slightly to moderately increased, with a reduction in the neutrophiles. Normoblasts are present. The granulocytes show a definite shift to the left. The red cells on blood smears are varied in size and shape, but there is no definite macro- or microcytosis. Poikilocytosis, anisocytosis, and polychromasia are absent. Hurwitt,[6] in a report of the subject, recorded 30 cases, 14 of which occurred during pregnancy. He concluded that the pregnancy may not have been coincidental, but that it may have played an etiological conditioning role.

Case Report

A 29-year-old white woman, gravida ii, para i, was admitted to the Cook County Hospital on May 31, 1944, with the history that at 8:00 A.M. she awoke feeling weak and dizzy, went to the bathroom and fainted. When she recovered she had severe epigastric pain.

Her last menstrual period occurred on May 20, 1944; it was very profuse and lasted seven days. Ordinarily her periods were every twenty-eight to thirty days and of five days' duration. Her occupation was that of a factory radio worker, in which she ground quartz crystals using carbon tetrachloride. In the previous ten days she had noticed that her gums bled easily.

The physical examination revealed a very anemic patient who appeared acutely ill. The blood pressure was 114/46, temperature 100.6° F., pulse 100, and respirations 24. On auscultation a soft systolic apical murmur was heard. On her back were several small areas of ecchymosis. On abdominal palpation, there was tenderness in both lower quadrants. Pelvic examination revealed tenderness in both adnexal areas with bulging into the cul-de-sac. The cervix and uterus were normal. The blood examination showed 690,000 erythrocytes, 2,200 leucocytes, 35 per cent hemoglobin, and a color index of 0.4.

The impression was ruptured ectopic pregnancy; a blood dyscrasia was considered. When 20 c.c. of blood were easily obtained by colpocenteses of the posterior cul-de-sac, the former diagnosis was supported and a laparotomy was done, the patient first receiving blood and plasma. The pelvis was full of fresh dark blood, the uterus, tubes, and ovaries were normal except for bleeding from the ostium of the left tube, which on stained section later proved to be normal microscopically. A left salpingectomy was done, the idea of a tubal abortion being entertained.

Following surgery another transfusion was administered and for three days the patient's condition steadily improved and was satisfactory. On the fourth day she became somewhat icteric and developed petechiae of the forearms, gums, and conjunctivae. A blood dyscrasia was again considered and a hematologist consulted. At this time the erythrocytes were 2,240,000, leucocytes 2,200, hemoglobin 23 per cent, platelets 125,000, icteric index 40, cevitamic acid level 35, nonprotein nitrogen 29, uric acid 3, and chlorides 580. The blood cultures were negative. The fundoscopic examination showed a hemorrhagic retinitis. A sternal puncture done on June 8 gave the following findings: "Marrow for the most part fibrotic with an incomplete disappearance of normal cellular elements. These cells do not appear young. Throughout the marrow one finds an occasional group of what appear to be diplococci. The opinion is that the material represents an aplastic marrow with secondary lymphoid degeneration as evidenced by the maturity of the cells seen." Thus a diagnosis of aplastic anemia was made.

In spite of repeated transfusions, vitamins C and K, iron and liver, the patient ran a downhill course and on the nineteenth postoperative day, when her temperature went to 106° F., she expired. An autopsy was performed and the following findings reported: hemorrhagic diathesis; petechial hemorrhages of all serous surfaces, skin and conjunctiva; hemorrhage into the right auricle and auricular appendages, edema of lungs; diffuse bronchopneumonia of both lungs; extreme gas formation in all organs, especially liver and spleen (a direct smear from the peritoneal cavity showed *B. welchii*—order of same present); hemorrhagic gastritis, hematometrium with blood coming from right tube; free blood in pelvis.

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HYDATIDIFORM DEGENERATION OF PLACENTA, COMPLETE WITH FETUS

ABE CLINE, COMMANDER, MC, USNR, JACKSONVILLE, FLA.

MRS. L. R., 18-year-old white married woman, was admitted to the Navy Dependent Hospital on Feb. 26, 1945, complaining of cramps and vaginal bleeding. Her last normal menstruation began in September, 1944. Irregular bleeding started two weeks before admission and continued intermittently until Feb. 25, 1945, when it became continuous and more profuse. She had experienced cramplike pains for several hours.

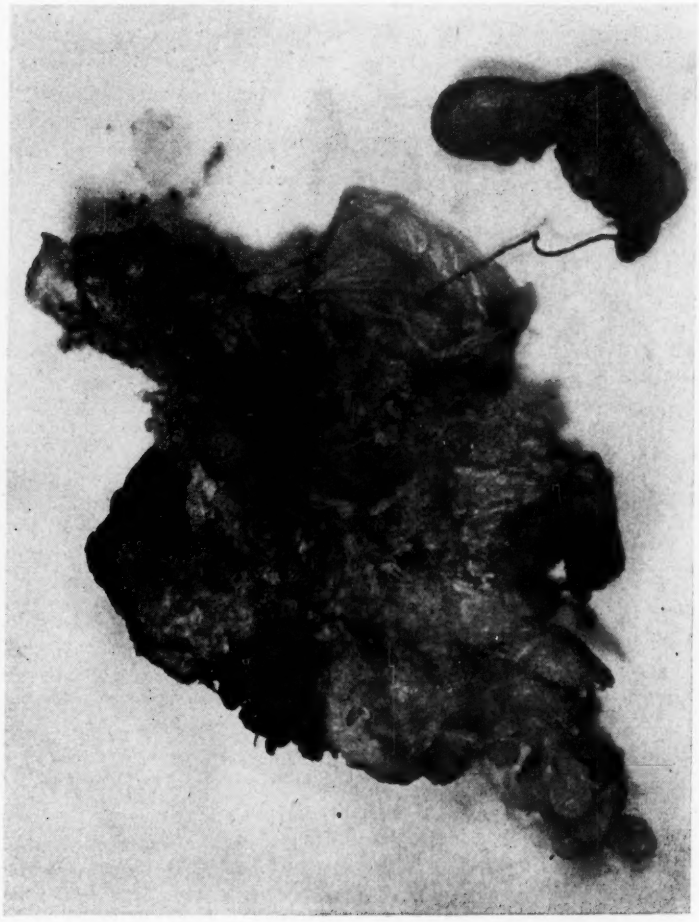

Fig. 1.

On admission, vaginal bleeding was moderately profuse. Ergotrate, 1/320 grain, was ordered three times a day, and codeine with aspirin for pain. Later, on examination, a dark red, firm, clotlike mass presented just within the vulvar orifice. It was removed with a sponge forceps. Grossly, the mass seemed to be placental tissue and was sent to the pathologic laboratory. The pathologist reported finding hydatid vesicles, whereupon I performed a curettage. A moderate amount of endometrium and clots were obtained.

More careful inspection of the original specimen showed that it included a small, papyraceous fetus within a sac, attached by an umbilical cord to a placenta which had undergone partial hydatidiform degeneration. The complete pathologic report by Lt. Comdr. Carl L. Minier follows:

Macroscopic Report.—Placenta measuring approximately 10 cm. in diameter is studded with numerous pedunculated cystic structures ranging from 2 mm. to 1 cm. in diameter. The amniotic sac which is attached contains a tiny, macerated fetus, "folded," and approximately 4 cm. in length, deep brown in color, which is attached by an umbilical cord 8 cm. in length, and less than 1 mm. in diameter.

Microscopic Report.—The placental villi are markedly enlarged and markedly edematous. There is considerable hyperplasia of the syncytium, the cells of which are enlarged, pale-staining, and show considerable vacuolization of the cytoplasm. Many of the distended villi form what appear to be small cystic structures containing small amounts of fibrin and filled with clear fluid. There is no evidence of malignant change.

Diagnoses.—(1) Hydatidiform mole, (2) degenerated fetus, six to eight weeks.

The specimen is of interest in that it shows a fetus of six to eight weeks' size, with a placenta of about sixteen weeks' size.

The patient made a prompt recovery and has had very little bleeding since. Friedman tests have been negative to date, but she will remain under observation.

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Department of Reviews and Abstracts

Review of New Books

Obstetrics and Gynecology

H. J. Stander's third revision of Williams' **Obstetrics**[1] constitutes the ninth edition of this classic American textbook, the first six of which were prepared by the late Dr. J. Whitridge Williams, the well-known professor of obstetrics at the Johns Hopkins University School of Medicine. The work has been given a new title, **Textbook of Obstetrics**, but continues to carry out the original significance as a book for students and practitioners. Many changes and additions have been made both in text and illustrations, among which attention may be drawn to the following:

The general organization has been revised and improved through the utilization of the newer and more popular plan of sections with subheadings. Considerable data have been added concerning the developmental anatomy, neurology, endocrine physiology, and development of the ovum. Teaching of the mechanisms of labor for the various presentations has been facilitated by the replacement and addition of several illustrations. The section on amnesia, analgesia, and anesthesia in labor has been extensively revised, including discussion of the newer drugs and techniques. The general subject of the complications of pregnancy has been rewritten nad brought up to date, including the section on toxemias.

Some medical schools teach only clinical pelvimetry and clinical or etiological classifications of contracted pelves, while others limit their instruction to morphologic classifications based on x-ray pelvimetry, these topics have been presented in separate subsections, and each is fully discussed.

Additions have been made in the section devoted to operative procedures and new illustrations have been added. Finally, the subjects of puerperal infection and diseases of the puerperium have been revised to include the newer methods of therapy.

This excellent presentation, devoted to an important and major branch of medicine, is well worthy of the attention which has been extended to previous editions. It remains the classic volume in American textbook literature on the subject.

GEO. W. KOSMAK.

The Management of Obstetric Difficulties, by Dr. Titus,[2] offers an extensive discussion of the abnormal conditions which may develop during the reproductive process. The broad viewpoint held by the author is reflected in the inclusion of chapters on sterility, late complications of the puerperium, and accidents, birth injuries, and asphyxia of the newborn. There is much material in this revision on x-ray pelvimetry, which is well illustrated; and the toxemias of pregnancy, for which the author proposes a new classification. In the discussion of analgesia and anesthesia in labor, the technique of Hingson and Edwards has been included in detail. The method is not, however, placed on the list of the author's preferences

[1]**Textbook of Obstetrics (Formerly Williams' Obstetrics).** By Henricus J. Stander, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College; Obstetrician and Gynecologist-in-chief, The New York Hospital; Director, New York Lying-In Hospital, New York City. D. Appleton-Century Co., New York. 1945.

[2]**The Management of Obstetric Difficulties.** By Paul Titus, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh. Third Edition. 976 pages. 426 illustrations and 8 color plates. The C. V. Mosby Company, St. Louis. 1945.

for relief of pain in labor, barbiturates and scopolamine being given as first choice. The limitations and disadvantages of the various types of cesarean sections are brought out in the section on obstetric operations. The techniques of extraperitoneal cesarean section are fully illustrated. The author discusses the use of penicillin and the sulfonamides in the various puerperal infections, while the Rh incompatibilities are warned against in the section on transfusion. The volume should provide a quick and practical aid to the solution of obstetric difficulties and emergencies.

PHILIP F. WILLIAMS.

The monograph **The Foetal Circulation and Cardiovascular System, and the Changes They Undergo at Birth** by Alfred E. Barclay, Kenneth J. Franklin, and Marjorie M. L. Prichard[3] is outstanding in that it describes the first direct recording of the blood flow in an intact fetus, an experiment which the authors performed in cooperation with Sir Joseph Bancroft and Dr. D. H. Barron.

The authors introduce their subject with a history of the four periods of views concerning the course of the fetal blood flow, including William Harvey's contribution. In the second part of the book they describe the actual course of the blood flow in the mature fetal lamb, as determined by means of cineradiography, a technique which they have perfected. In this section they describe the technique of the necessary operative procedure on the ewe. The method used is contrast media and a radiographic technique. The latter is a refinement and an advancement of the studies made in recent years of the peripheral cardiovascular system.

The third part of the monograph deals with the cardiovascular system and circulation in the mature fetal lamb. Here one finds a glossary of new names which they have substituted in this study for certain parts of the fetal cardiovascular system. The physiologic changes occurring at birth of the lamb are fully discussed. This excellent description of the subject as it relates to the sheep is succeeded by comparative studies in other animals.

The fifth and final part of the book describes the subject as it is applied to the human fetus from our present knowledge of its physiology before birth and the anatomic changes which occur at birth or shortly thereafter. The authors list some of the factors which would complicate a human study of a similar nature. The principal stumbling block to the use in the human of such techniques would undoubtedly be the need for the parents' consent. They suggest, however, that in some such situation as the discovery beforehand that the fetus was abnormal, as an anencephalic monster being diagnosed by roentgen ray, a favorable instance of such a study would be occasioned. There are also discussions in a closing chapter of the various factors concerned with the closure of certain fetal channels. The monograph is a detailed and well-documented study of an important anatomic-physiologic problem.

PHILIP F. WILLIAMS.

In **The Physiology of the Newborn Infant** Dr. Smith[4] discusses the profound changes and rapid adaptations of the bodily systems at the time of birth. The importance of these adjustments and alterations has been recognized, and here one finds a thorough description of the nature of the changes. In discussing the various systems, the fetal aspect of function is given first to contrast with the neonatal physiology. Of special interest are the chapters on fetal and neonatal respiration. There is an excellent presentation of fetal and neonatal nutrition which describes the assimilation and metabolism of specific food substances, which is followed by an equally important description regarding minerals and vitamins. One is intrigued that the endocrinology of the immediate newborn period has progressed to the high

[3]**The Foetal Circulation and Cardiovascular System, and the Changes That They Undergo at Birth.** By Alfred E. Barclay, O.B.E., F.R.C.P., F.F.R., F.A.C.R., Kenneth J. Franklin, and Marjorie M. L. Prichard, M.A., of the Nuffield Institute for Medical Research, Oxford Blackwell Scientific Publications, Ltd., Oxford. 1944.

[4]**The Physiology of the Newborn Infant.** By Clement A. Smith, M.D., Professor of Pediatrics, Wayne University College of Medicine; Medical Director, The Children's Hospital of Michigan. First edition. 294 pages. Charles C. Thomas, Springfield, Illinois. 1945.

plane of scientific investigation noted. An important maternal-fetal relationship, in connection with the Rh factor is discussed at some length in the chapter on neonatal immunology.

A helpful feature of the book is a concise and quite practical résumé following each chapter, as a clinical summary. Obstetricians and Pediatricians will find in this volume an excellent discussion of the physiology of the natal period which should be helpful in understanding the problems of the immediate newborn child.

PHILIP F. WILLIAMS.

After seventeen years of publication in three editions Dr. Stone's **The New-Born Infant,**[5] a manual of obstetric pediatrics, bids fair to becoming an obstetric classic. The aims of this book are to present the pertinent data from the literature, and to emphasize the obstetrician's viewpoint and responsibility for the newborn infant. The present edition is a fine working manual of neonatal physiology and pathology, which expresses concisely the rational principles of care, feeding methods, early diagnosis, and modern treatment. Prenatal influences and birth trauma are the province of the obstetrician; for his benefit the diseases of the neonatal period are thoroughly discussed. The present status of penicillin is mentioned, Rh factor is considered at length, and then there is a review of the hemorrhagic diseases. The care of the premature is detailed. One might wish for more frequent personal opinions by the author. The introduction is an interesting summary of preventive work in obstetrics and pediatrics in recent years. The book should be particularly valuable to the obstetrician who has no pediatrician for his newborn nursery.

PHILIP F. WILLIAMS.

This short monograph[6] is a doctoral thesis which deals with the opthalmoscopic and capillaroscopic findings in pregnancy toxemia. These positive findings are supposed to be of great diagnostic help. The thesis is based on nine cases. There are a number of colored charts showing the eye grounds and skin capillary changes.

R. T. FRANK.

Recent Advances in Obstetrics and Gynaecology by Bourne and Williams[7] is the sixth edition, appearing in three years after the fifth one. Like its predecessors, this is a sterling, well-planned book. Much has been rewritten. Many chapters have been added. Among the new chapters are Nutrition in Pregnancy, Vitamin K, Stillbirth, Neonatal Death, and Erythroblastosis; a chapter on X-ray therapy in gynecology by Levitt, which is now separated from the chapter on Radiological Diagnosis. The chapter on Ovarian Tumors is by Wilfred Shaw, the Radiological Investigation and Diagnosis in Gynecology, by Rohan Williams.

These English books show more coherence and continuity than our American yearbooks. They do this at the expense of not including the more recent literature.

R. T. FRANK.

Perez and Blanchard present a faultlessly gotten up monograph on Vaginal Trichomoniasis[8] which represents eight years of study. Every aspect of the subject is taken up in detail, with a very thorough presentation of the world literature. Both colored and black and white

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[5]**The New-Born Infant.** A Manual of obstetric pediatrics. By Emerson L. Stone, M.D., Associate Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale University; Attending Obstetrician and Gynecologist to the New Haven Hospital. Third Edition. 297 pages. Lea and Febiger, Philadelphia. 1945.

[6]**Patologia Vascular de las Toxicosis Gravidicas.** Examen oftalmoscópico, capillaróscopico y microscópico postmorten, de los vasos finos de las mujeres con intoxicaciones del embarazo. Por Angel Martinez de La Riva Labarta. 80 pages. Imprenta Moret. La Coruna.

[7]**Recent Advances in Obstetrics and Gynaecology.** By Aleck W. Bourne, M.A., M.B., B.Ch. (Camb.), F.R.C.S. (Eng.), F.R.C.O.G., and Leslie H. Williams, M.D., M.S. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G. Sixth edition. 77 Illustrations. 357 pages. The Blakiston Co., Philadelphia. 1945.

[8]**Tricomoniasis Vaginal.** By Manuel Luis Perez and Oscar Blanchard. 173 pages. "El Ateneo," Buenos Aires. 1944.

illustrations are especially good and instructive. The innumerable methods of treatment which have been published are described, the authors not expressing any very definite personal views as to what they favor. For those who read Spanish, this will prove to be a most instructive monograph.

R. T. FRANK.

Endocrinology

This is an important monograph written by Mme. Moricard,[9] who, for years before her marriage, had worked with her husband in both the laboratory and clinic. The material is based on six hundred cases studied at the gynecologic clinic of the Hospital Broca. This monograph gives one a summary of the best in French sex endocrinology that has appeared in years. Moricard is known to many of us because he spent some time in traveling throughout the United States and Canada in 1936. His main interest experimentally has been the study of the minute cytology of changes induced by the various sex hormones in the ovary and the rest of the genital tract.

This extensive, well-organized, and well-illustrated monograph of three hundred and eighty-two pages, covers the subject in detail. It goes into the quantitative and qualitative assay of the various hormones, the pharmacology, and then takes up the sex steroids individually.

The second portion deals with the artificial development of the genital tract of the woman, which is based on the careful studies of R. Moricard. The subject of atrophies secondary to hypophysectomy are discussed; then, in detail, the artificial hormonal stimulation of the female genital tract in the human, including artificial menstruation. A good deal of attention is given to disturbances in balance in estrogen and androgen, between estrogen and progesterone, and the symptoms ascribable to these. So-called troubles due to the lack of receptivity, that is, a localized lack of response to hormonal stimuli, is an important and interesting phase of the discussion. Genital dystrophies due to hormonal changes are ascribed to conditions like fibroids, endometriosis, changes in the portio and in the breasts. Particularly attention is paid to contraindications in hormonal therapy.

This is an important monograph, as I have said, which is well worth studying. I naturally find many points of disagreements, but certainly admire the care shown in the detailed studies, the conservative viewpoint, both in making diagnoses and in planning therapy. Anyone interested in sex endocrinology will certainly profit by reading this volume.

R. T. FRANK.

The second edition of Julius Bauer's **Constitution and Disease**[10] has appeared after three years. As the subtitle says, this deals with applied constitutional pathology. Bauer, when professor of medicine at the University of Vienna, attracted a large American postgraduate contingent. His popular appeal continues now that he is professor of clinical medicine in Los Angeles, California. The author states that nothing can "replace the impression gathered from an intelligent observation of the patient himself." Leaving this out of consideration accounts for the fact that frequently patients, who are run through the diagnostic mill in certain clinics, are not benefited by the thorough study because there is a lack of final integration. The object of the book is to stimulate medical thinking, a supplement to the routine medical curriculum. The genetic basis and the tremendous variation in what

[9] **Hormonologie Sexuelle Humaine.** Physiologie Pathologie Thérapeutique. par Mme. F. Moricard. Chargée de la consultation d'endocrinologie de la Clinique gynécologique de Paris. Préface de R. Moricard, Chargé de maitrise de conférence à la Faculté des Sciences de Caen. Directeur à L'École des Hautes Études. 382 pages. Masson et Cie, Paris. 1943.

[10] **Constitution and Disease.** Applied Constitutional Pathology. By Julius Bauer, M.D., Professor of Clinical Medicine, College of Medical Evangelists, Los Angeles; Senior Attending Physician, Los Angeles County General Hospital; Consultant in Medicine, Cedars of Lebanon Hospital, Los Angeles; formerly Professor of Medicine, University of Vienna. Second Edition. Revised and enlarged. 247 pages. Grune & Stratton, Inc., New York. 1945.

may be considered normal is emphasized in contradistinction to the similarity noted in uniovular twins in whom even the electric brain waves are either identical or very much alike. Many important subjects are taken up. I instance merely congenital malformations, individual differences in response to the same factors, sex-linked traits. An important chapter deals with constitutional biologic inferiority of the various organs and tissues of the body.

This book is an important and interesting contribution which can be read with great profit by both medical students and practitioners.

R. T. FRANK.

This short monograph[11] was accorded the "Madame Durocher Prize" by the National Academy of Medicine, 1944. It is a summary of the quantitative methods of evaluating the gonadotropic and estrogenic hormones. The world literature is given in considerable detail. Concise but understandable directions describing each method are presented. The final chapter includes the method of pregnancy diagnosis.

R. T. FRANK.

Miscellaneous

The March of Medicine[12] is a small brochure which records the ninth year of lectures to the laity. The object of these lectures is to present to the laity through experts and authorities in the field, aspects of medical science which are too often misrepresented in the press, on the radio, and other sources of public information.

Among the subjects dealt with are Morale and Propaganda by Strecker; Food and Civilization by Charles Glen King; a very illuminating talk on the Past, Present, and Future of Chemotherapy by MacLeod; a Survey of Medicine and the Changing World by Fitz; a semi sermon on the Effects of Science upon Human Beings by Sir Gerald Campbell; and a concluding talk on Wars and Epidemics by Lieutenant Colonel Mackie.

These lectures should prove as interesting to the medical profession as to the lay public.

R. T. FRANK.

Stern has written a book on **Trauma in Internal Diseases**[13] with consideration of experimental pathology and medicolegal aspects. The author mentions that there are some ten million accidents a year in this country and many of them are allegedly the cause of ensuing internal diseases. War is certainly multiplying the number of such cases. A final responsibility for obtaining fair adjustment of claims, fair to both the injured and to the insurer or taxpayer, is the medical profession. The author hopes that this book will help the practitioner in performing this task.

The entire subject of internal disease is supposed to be covered. This includes not only the infectious diseases but also the diseases of the heart and circulation, of the lungs, in fact, of all the contents of the thoracic cavity. Next are taken up the diseases of the stomach and duodenum, as well as that of the intestine and the appendix; also those of the peritoneum. Subsequently diseases of the liver and the ducts, and diseases of the pancreas and kidney are covered. Malignant neoplasm of the internal organs are dealt with. Then there are diseases of the metabolism, mainly of diabetes, followed by diseases of the endocrine glands. The concluding chapter covers diseases of the blood and lymphatic system.

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[11] **Hormonios Gonadotróficos E Estrogênicos.** Sua Avaliacão Quantitativa. Trabalho laureado com o "Prêmio Madame Durocher," pela Academia Nacional de Medicina (1944), by Clarice Do Amaral. 43 pages. Gráfica Sauer, Rio de Janeiro. 1944.

[12] **The March of Medicine.** The New York Academy of Medicine Lectures to the Laity, 1944. 121 pages. Columbia University Press, New York. 1945.

[13] **Trauma in Internal Diseases.** With Consideration of Experimental Pathology and Medicolegal Aspects. By Rudolf A. Stern, M.D., Assistant Attending Physician, City Hospital, New York City. Foreword by Francis Carter Wood, M.D., Director of Laboratories and Radiotherapy Department, St. Luke's Hospital, New York. 575 pages. Grune & Stratton, Inc., New York. 1945.

The book is well planned, contains innumerable illustrative cases and case histories, emphasizes the exact pathology, and in some cases quotes court decisions. The material dealt with is extremely large, and is documented by an extended bibliography. From the point of view of our readers, it is noticeable that neither the male nor the female sex organs are considered, although these not infrequently fall into the category of claims following injury. If these omissions were not present, I would consider the book extremely satisfactory.

R. T. FRANK.

The second volume of Dr. Helene Deutsch's **Psychology of Women**[14] on Motherhood is an extremely interesting book. In this thorough psychoanalytic interpretation of womanhood Dr. Deutsch has studied the reproductive process from an entirely new angle. She explains here the emotional factors and conflict situations which come into relation with pregnancy as a whole, and with the organic manifestations characteristic of pregnancy. While many of the psychic problems of pregnant women are difficult of interpretation, the physician will more thoroughly understand the factors which produce them from a study of this text. The attitude of many women toward delivery, and their extreme interest in obstetric analgesia is well discussed in the chapter on delivery. Dr. Deutsch discusses various methods of amnesia and analgesia in labor from the psychologic viewpoint. The related problems of maternity are well considered in the three chapters on the psychologic attitudes of illegitimacy, adoption, and step-motherhood. The volume could be read with profit by all obstetricians.

PHILIP F. WILLIAMS.

This interesting **History of Surgical Anesthesia** by Thomas E. Keyes[15] is an outgrowth of historical research developed for a chronologic table for a recent text on anesthesia. Dr. Chauncey D. Leake has written a delightful introduction to the book, replete with anecdotes and intimate reminiscences concerned in the discovery of recent anesthetic agents. Mr. Keyes goes back through the ages to start his history of anesthesia, and quotes from prose and poetry to give the earliest references to various methods which were used to promote relief from pain. The trials and tribulations in early attempts at inhalation anesthesia and the battles over priority are fittingly illustrated, with excellent pictures of the men of that time, whose names live on today. Mr. Keyes recounts the historical facts associated with development of the various types of anesthesia as we know them today. It appears that scopolamine-morphine was first used in obstetric practice in 1902, and mention is made of other anesthetic methods in obstetrics, including the presently popular caudal block.

The history of anesthetic apparatus is also recorded in the volume. There is an extensive bibliography, and a look into the future by Noel A. Gillespie, which suggests the intellectual opportunities of this still young specialty. The volume should be of interest to all those in the surgical field.

PHILIP F. WILLIAMS.

In this fourth edition of his **Synopsis of Genitourinary Diseases** Dr. Dodson[16] presents essential facts of urology in a concisively styled text for the medical student, and as a handy reference for the physician in practice. The first four of the fourteen chapters in which the text is divided discuss diagnosis, minor procedures, anatomy, and the anomalies. The remainder of the book deals with the various disease of the urological tract. Among the evident revisions to which the previous text has been subjected are the discussions of the sulfonamides in the therapy of urological infection, and the present knowledge of penicillin in

[14] **The Psychology of Women.** A Psychoanalytic Interpretation by Helene Deutsch, M.D., Associate Psychiatrist, Massachusetts General Hospital Lecturer, Boston Psychoanalytic Institute. Volume Two, Motherhood. Grune & Stratton, Inc., New York. 1945.

[15] **The History of Surgical Anesthesia.** By Thomas E. Keyes. Schuman's, New York. 1945.

[16] **Synopsis of Genitourinary Diseases.** By Austin I. Dodson, M.D., F.A.C.S., Professor of Genitourinary Surgery Medical College of Virginia. Fourth Edition. 296 pages. The C. V. Mosby Company, St. Louis. 1945.

similar conditions. The author is quite moderate concerning the use of stilbestrol and castration in the treatment of carcinoma of the prostate. General principles enunciated regarding many topics in this volume should be of value to the obstetrician and gynecologist.

PHILIP F. WILLIAMS.

Dr. Walter L. Bierring has edited the fifth edition of **Rypins' Medical Licensure Examinations.**[17] The original plan of separate summaries of each subject and actual questions based on the essential facts has been maintained. A new section of Pharmacology has been added. In a foreword Dr. Bierring discusses the philosophy of examinations, which is of interest considering the multitudes of examining boards for both ordinary practices and specialization in this country. Each of the sections into which the text is divided has been reviewed by an outstanding authority on the subject; Dr. Eastman of Johns Hopkins has reviewed the section on Obstetrics and Gynecology. This book is highly recommended for the recent graduate taking State Board Examinations, but it would be of much less assistance to the candidate for a Specialty Board.

PHILIP F. WILLIAMS.

Ribeiro has written a monograph on Lithiasis of the Appendix Vermiformis[18] covering the world's literature, diagnosis, surgical importance, etc. Between 43 and 63 per cent of the cases discovered have been in gangrenous appendices. The author reviewed the Brazilian cases, and adds one case of his own.

R. T. FRANK.

Leon[19] has published a lengthy account of his short incumbency as directory general of public health in the province of Buenos Aires. The volumious and detailed presentation may be of interest to those occupied with public health problems, but has little appeal to the general medical reader.

R. T. FRANK.

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[17]**Rypins' Medical Licensure Examinations.** By Walter L. Bierring, M.D., F.A.C.P., M.R.C.P., Edin. (Hon)., Member, National Board of Medical Examiners; Secretary, Federation of State Medical Boards of the United States; with the collaboration of a Review Panel. Fifth Edition. 530 pages. J. B. Lippincott Company, Philadelphia. 1945.

[18]**Litíase do Apêndice.** By Eurico Branco Ribeiro, Director do Sanatório São Lucas. 87 pages. Sociedade Editora Médica Limitada. São Paulo, Brasil. 1943.

[19]**La Dirección General de Higiene de la Provincia de Buenos Aires.** Algo de la labor desarrollada especialmente en el terreno de la Protección Maternal e infantil. By Dr. Juan Leon, Ex-Director General de Higgiene de la Provincia de Buenos Aires. 203 pages. "El Ateneo," Buenos Aires. 1944.

Selected Abstracts

Malignancies

Bromberg, Y. M., and Brzezinski, A.: Primary Melanosarcoma of the Vagina, J. Obst. & Gynaec. Brit. Emp. **51**: 147, 1944.

The authors report this case of rare tumor of the vagina in a woman 68 years old. The patient was treated with x-ray and radium with improvement for the first six months. The patient developed another tumor on the posterior wall of the vagina. There were no other signs of metastasis in the body. One year after her initial treatment she developed pulmonary metastasis and one month later she developed osseous metastasis and died shortly thereafter.

WILLIAM BERMAN.

Peralta Ramos, Alberto, Albertelli, Jorge F., and Colombo, Emilio: Value of Quantitative Determinations of Gonadotrophin in the Diagnosis of Chorionepithelioma, Bol. Soc. Chilena de obst. y ginec. **8**: 49, 1943.

The authors state that after eliminating the presence of a pregnancy, the diagnosis of chorionepithelioma may be established without losing time by the search for high values of gonadotrophin: 1,000 rabbit units per liter of serum are enough to indicate hysterectomy, especially if the curve is ascending. Evaluation of the amount of gonadotrophin present after molar pregnancy must be systematic to discover the presence of an active trophoblast capable of degenerating. The evaluation must be made in the serum; adult rabbits must be used for the test, and the unit should be that of Brindeau, Hinglais, and Hinglais.

The authors use the following technique after molar abortion or in cases of suspected malignant degeneration: weekly estimation of gonadotrophin in the serum, searching for 200 rabbit units; if the test is repeatedly negative for two months, the urine is investigated by the concentration method, searching for 50 units which are sufficient to reveal the presence of ovular remnants capable of degenerating. If the result remains negative, the diagnosis of chorionepithelioma is rejected. If in the estimation of the blood the amount of 200 units is found, the tests are repeated weekly to obtain a curve, and if the variation is over 500 units as a minimum, even when the increase in the curve is slow but progressive, the diagnosis of chorionepithelioma is made after elimination of the possibility of a new pregnancy.

J. P. GREENHILL.

Endocrinology

Scheffey, Lewis C., Farell, David M., and Hahn, George A.: The Role of Injudicious Endocrine Therapy, J. A. M. A. **127**: 76, 1945.

The authors discuss the use of endocrines in cases of abnormal uterine bleeding without complete physical examination, especially complete pelvic examination. The authors do not wish to discount or disparage the possible benefits of carefully controlled endocrine medication. Its use in the management of functional bleeding of adolescence and in the early reproductive period is permissible providing the patient has been completely and thoroughly examined and no organic reason has been found for the bleeding. When abnormal bleeding is present during the late reproductive, menopausal, or postmenopausal periods, there is much less justification for prolonged and experimental endocrine therapy. Procrastination is inadvisable in these cases. Delayed diagnoses of both benign and malignant conditions of the pelvis are often due to the use of endocrine products without preliminary examination to exclude organic pelvic disease.

WILLIAM BERMAN.

Schaffer, Bernardo: Intravenous Pituitary Extract, Bol. soc. de obst. y ginec., Chile 23: 79, 1944.

The experience of the author shows that this procedure is a valuable medication which should only be used on precise indication and in serious cases. Although he does not believe that it jeopardizes the life of the patient, he uses it with caution because he considers it as an active medication which may offer some risks.

It is prudent to replace the intravenous route by injection into the cervix or uterine body when possible. Injection into the cervix is easy; it is sufficient to push the uterine fundus down through the abdominal wall to make the cervix appear at the vulva, especially in multiparas. In any case, it is preferable to use a minor vaginal maneuver to reach the cervix than to inject through the abdominal wall. In cesarean section intramuscular injection is preferred.

If attempts by these routes fail, the intravenous method is indicated to control hemorrhage due to atony which is its principal indication. The method should not be used routinely to separate the placenta because the saving of about fifteen minutes does not compensate for even the remote risk incurred.

J. P. GREENHILL.

Endometriosis

Orfila, J. P.: Diagnosis and Treatment of Endometriosis, Paper presented at the Fifth Argentine Congress of Obstetrics and Gynecology at Buenos Aires, Oct. 3 to 8, 1943.

In this monograph the author takes up all the aspects of endometriosis. He believes that mechanical, irritative, and inflammatory hormonal factors are involved in the etiology. He found endometriosis in approximately 10 per cent of the patients he operated on.

The principal symptoms of endometriosis are pain, which depends on the location of the lesions and includes dysmenorrhea, excessive bleeding at the menses, sterility, and dyspareunia.

Treatment is both prophylactic and curative. Among the prophylactic measures are proper drainage of the uterus, obtained by overcoming cervical stenosis and correcting uterine retroflexions. Active therapy consists of surgical removal of the involved tissue and radiation therapy. The age is an important consideration as to which treatment is chosen. Occasionally, both surgery and radiation must be employed.

J. P. GREENHILL.

Sammartino, R., and Gori, R. M.: Tubal Pregnancy and Endometriosis, An. brasil de ginec. 17: 85, 1944.

The authors report a series of 100 cases of ectopic pregnancy studied by serial sections. In 11 cases they found typical endometriosis in the tubes, and in 5 additional cases there were islands of endometriosis associated with the tubal sac. In 31 cases there was a typical decidual reaction. The authors are of the opinion that the incidence of endometriosis in their 100 cases is 42 per cent because they add the cases of decidual reaction to those showing typical endometriosis.

J. P. GREENHILL.

Miller, James Raglan: Preoperative Use of Testosterone Propionate as an Aid to Surgical Treatment of Endometriosis, J. A. M. A. 125: 207, 1944.

The author reports a case of endometrioma of the pelvis which bulged into the rectal wall, which was reduced in size by the preoperative injection of 25 mg. testosterone propionate (24 injections given twice weekly). The mass was removed together with the uterus and a portion of the rectal wall which the tumor had invaded. It had not perforated the lining epithelium. The patient made an uneventful recovery.

WILLIAM BERMAN.

Labor

Peiretti, F. S., and Rabinovich, O.: Labor in Breech Presentation, An. ateneo Inst. mat. y asist. 389-403, 1943.

The authors report that breech presentation occurred in 5 per cent of all labors attended to at the Institute during the decade 1934 to 1943. The presentation was complete in 44.1 per cent and incomplete in 55.9 per cent. In the complete form there were 31.8 per cent young primiparas, 8.2 per cent old primiparas, and 60 per cent multiparas; in the incomplete form there were 36.8 per cent young primiparas, 12.2 per cent old primiparas, and 51 per cent multiparas.

Birth was spontaneous in 88.2 per cent: 90 per cent in the young primiparas, 77.9 per cent in the old primiparas, and 89.1 per cent in the multiparas. Birth was spontaneous in 65 per cent of pelvic deformities with breech presentation.

The fetal mortality rate was 19.1 per cent. Elimination of immature, malformed, and macerated fetuses reduced the rate to 10.5 per cent.

The maternal mortality rate was 0.8 per cent, the corrected rate being 0.08 per cent.

J. P. GREENHILL.

Mackie, Margaret A.: Comparison Between Surgical Induction of Labour by Means of the Rectal Tube and Surgical Induction of Labour by Artificial Rupture of the Membranes, M. J. Australia 2: 428, 1944.

This study covers a period of six years, and in each case pregnancy had advanced to at least the twenty-eighth week. The maternal mortality rate in rectal tubal induction was 2.5 per cent while in artificial rupture of the membranes it was 0.5 per cent. Using the accepted standard of morbidity it was found that the rectal tube method of induction gave a morbidity of 17.2 per cent while in artificial rupture of membranes it was 13.5 per cent. The total fetal mortality for tubal induction was 37.2 per cent, while for artificial rupture of membranes it was 19.2 per cent. From 34 weeks' gestation onward the fetal mortality rate is considerably lower when labor is induced by artificial rupture of the membranes, while under 34 weeks' gestation there is no significant difference between the results of the two methods. The time from induction to delivery after artificial rupture of membranes is lower than that after tubal induction in all groups.

WILLIAM BERMAN.

Menopause

Lane, Frederic E.: Menopausal Therapy in Clinic Practice, West. J. Surg. 52: 313, 1944.

A comparison of the clinical response to estradiol benzoate (parenteral) diethylstilbestrol (oral), and hexestrol-phenobarbital (oral) was made on 358 patients with menopausal symptoms. In evaluating results, conclusions were based entirely on subjective response. The estradiol group showed that 83 per cent improved, the diethylstilbestrol group showed improvement in 49 per cent, and the hexestrol group gave a 67 per cent improvement. Best results were obtained with the estradiol group, but the expense of the material and the inconvenience of the injection method caused the authors to adopt the hexestrol-phenobarbital. Their incidence of nausea was 7 per cent and they attribute this low incidence to the presence of phenobarbital in the mixture. Nausea was definitely higher in the stilbestrol group and results definitely inferior.

WILLIAM BICKERS.

Gynecology

Pommerenke, W. T.: Criteria of Ovulation, West. J. Surg. 52: 416, 1944.

A relatively complete history of the evolution of our knowledge relative to ovulation is presented. Man's kinship with other mammals in relation to physiologic changes incident

to ovulation is discussed. The affinity of all the basic science to physiology is emphasized. The means by which this knowledge can be used for the diagnosis of ovulation in the human being are reviewed.

Examination of the corpus luteum at the time of operation gives information as to the probable age of the corpus luteum, and, therefore, the date of ovulation. The theory that ovulation is accomplished by a change in the electric potential between the abdomen and vagina has been used in an effort to determine ovulation time. Normally, the vagina is negative to the abdominal wall by 10 millivolts, and at time of ovulation the vagina becomes positive by 30 millivolts. Various investigators reported conflicting results, and, therefore, it is probably true that a recording apparatus is not sufficiently sensitive to make this a practical clinical procedure.

The rabbit's uterus is extremely sensitive to Pituitrin before ovulation. Following ovulation, the uterus is refractory to pituitrin. Although this is not true in the human being, the pattern of uterine contractions in the human being during the luteal phase is different from that in the follicular phase.

The secretory changes of the endometrium during the luteal phase of the menstrual cycle is the best clinical indicator that ovulation has occurred. The characteristic endometrial picture of secretory phase consists of dilated and distorted glands, stromal edema, vacuolization of the cells, and secretion of the lumen.

Clear, translucent, cervical mucus appears at the time of ovulation in the human. This mucus has been demonstrated to be more permeable to spermatozoa than cervical mucus at other times of the cycle.

The vaginal smear has been used for the diagnosis of ovulation. A sudden increase in leucocytes and cornified cells, particularly when associated with erythrocytes, is diagnostic. By this means the general time, but not the exact moment, of ovulation can be determined.

Cyclic temperature changes occur during the ovulatory cycle in woman. Basal rectal temperatures during the ovulatory cycle show a biphasic curve. During the first half of the cycle, the temperature is relatively low, rising to a peak at ovulation time, followed by a relatively high level during the luteal phase, and dropping again just before menstruation.

From the evidence at hand it appears that ovulation in women occurs about fourteen days before the next expected menstrual period.

WILLIAM BICKERS.

MacFarlane, Catherine, Sturgis, Margaret C., and Fetterman, Faith S.: The Value of Periodic Pelvic Examination, J. A. M. A. 126: 877, 1944.

The authors undertook to determine the value of periodic pelvic examination in the detection of cancer of the cervix in an early stage and also the detection of inflammatory lesions of the cervix which predispose to cancer. A total of 9,111 pelvic examinations were made over a six-year period. During the last two years of this survey the breasts were also examined. In the course of these examinations 18 cancers of 10 different organs were discovered by or reported to the authors. In 461 of the inflammatory lesions found, treatment seemed necessary and was advised in 295 of them, and treatment was carried out in 200 cases. The authors preference was for the Sturmdorff trachelectomy. The authors are thoroughly convinced of the value of the above procedure in trying to eradicate malignancy.

WILLIAM BERMAN.

Pastorini, R., Rabinovich, O., and Chavanne, F. C.: Transfusion of Preserved Placental Blood in the Treatment of Hemorrhagic Metropathies, An. ateneo. Inst. mat. y asist., 323-329, 1943.

The authors claim priority in the use of this method which has a double therapeutic action: specific to cure the endocrine dysfunction, and substitutive to correct the anemia. They recommend trial of the method in all cases of functional metrorrhagia of the puberal, genital, and premenopausal age, with the certainty that no time will be lost for the patient because, even in the worst cases, she will receive the benefit of substitutive therapy.

They report five cases. Three were juvenile metrorrhagias which were arrested by one 150 c.c. transfusion. In two of them the menstrual cycle was again started in regular form. The fourth was a case of Brenecke-Schroeder disease in a woman, 46, with intense anemia: the hemorrhage, which had lasted twenty-two days, stopped four hours after a 200 c.c. transfusion. The fifth case was that of a woman, 25 years of age, with acute anemia caused by a hemorrhage occurring after an amenorrhea of three months. Histologic study revealed an atrophic uterine mucosa. The hemorrhage, which had lasted several days, decreased markedly after a first transfusion of 320 c.c., and stopped after a second transfusion of 250 c.c. given thirty-six hours after the first.

J. P. GREENHILL.

Menstruation

Soares Baptista, J. A.: Premenstrual Tension, Rev. de ginec. e d'obst. **38**: 19, 1944.

In five cases, the author used the therapeutic method of Greenhill and Freed who obtained good results by eliminating salt from the diet and giving ammonium chloride, 0.60 Gm. three times a day, during the second part of the menstrual cycle.

In four patients the author obtained disappearance of the syndrome during the period of treatment. But the treatment gave little or sometimes no relief in the remaining patient who had a grave form of tension. Therefore, the advice of Frank was followed and the ovaries were irradiated to obtain temporary castration; this made all symptoms of tension disappear as long as the action of the rays lasted.

Bromides were administered as adjuvants during the worst days of tension.

J. P. GREENHILL.

Item

American Board of Obstetrics and Gynecology, Inc.

The following diplomate has been certified and is added to the previously published list: Dr. Max L. Berlowe, 315 Whitney Avenue, New Haven, Connecticut; born 1907; received M.D. from Long Island College of Medicine in 1934.

Paper in This Issue

Due to conditions beyond the control of the editors and publishers, this issue of the JOURNAL is printed on uncoated paper.

Correspondence

The Extraperitoneal Cesarean Section

To the Editor:

In his article (AM. J. OBST. AND GYNEC. 50: 191, 1945) Bourgeois states: "Extraperitoneal cesarean section is steadily gaining acceptance as the procedure of choice for abdominal delivery of potentially or actually infected parturients with obstructed labor." Few will find such a statement objectionable. Probably, few will consider Bourgeois' technique as "extraperitoneal." Few, very few, obstetricians will read the details of his case reports without being somewhat astounded. Some will wonder whether the description of a technique and the invention of a word to describe it will ever adequately replace sound obstetric judgment and reasonable obstetric courage.

Bourgeois presents ten brief descriptions of cases in which his technique was employed. In *eight* of these, from data presented by the author, reasonable indication for *elective* section was manifest at the time the cases were admitted to the hospital. In the other two cases certain facts are not presented and it is entirely possible that if they were included in the paper those cases too might have presented indications for elective section.

We have listed Bourgeois' cases, with his data, following each with a brief comment.

CASE 1.—"26-year-old primigravida . . . entered the hospital in early labor, roentgenologic examination disclosed a small gynecoid pelvis with evidence of cephalopelvic disproportion." The alternative to elective section in the presence of a small gynecoid pelvis is test or trial of labor. This patient was allowed 19 hours of "strong labor" twelve of them with the membranes ruptured. Why? Was it a trial of labor or endurance?

CASE 2.—". . . a small gynecoid-android pelvis with much molding of the unengaged head." In place of elective section this patient labored for 27 hours before section was performed. Why?

CASE 3.—". . . diagonal conjugate had measured 9.5 cm., and x-ray had disclosed a platypelloid pelvis." (This patient had previously delivered a baby spontaneously. The baby died in the neonatal period.) "After 10 hours of moderate labor without promise of engagement of the overriding head, pregnancy was terminated . . . by cesarean section, by election of the extraperitoneal type."

This patient, having had one baby die, presented a bad pelvis and an unengaged vertex. In place of prompt section, the baby was risked through 10 hours of labor. The condition of the membranes is not stated, but it is obvious enough that this patient did not require extraperitoneal section.

CASE 4.—"A 35-year-old primigravida . . . small gynecoid pelvis. Going into labor at thirty-nine weeks' gestation with a frank breech." This is sufficient indication for elective section for most obstetricians. The indication was not noted. Instead: "she made satisfactory progress until the cervix was completely dilated, after which the breech *failed to advance during a nine-hour period.*"* Is this to be believed? In 1945? Nine hours of the second stage of labor before intervention?

CASE 5.—"A 25-year-old primigravida . . . with a small gynecoid pelvis by both clinical and x-ray examination." This patient presented an unengaged vertex. Again reasonable indication for elective section or *humane* trial or test of labor. The author noted, "failed to engage the head after 27 hours of labor and eight hours of membrane rupture." He then delivered by extraperitoneal section (his technique) an 8-pound 12-ounce baby. A large baby and a small gynecoid pelvis call for elective section, not 27 hours of aseptic torture.

*Italics mine.

CASE 7.—"A 26-year-old primigravida . . . presented a small platypelloid pelvis with diagonal conjugate of 9 cm. . . . the head persistently overrode the symphysis." Cesarean section on admission to a hospital in such a case would evoke no criticism. The author did not determine in a matter of seconds by such a procedure as the "Hillis Impression" that the "head persistently overrode the symphysis." His patient was in labor for 17 hours before he decided upon section.

CASE 9.—"A 23-year-old primigravida at term presented an unengaged head after 38 hours of labor and an equal duration of membrane rupture." If this patient was admitted to the hospital in the first hours of labor, section should have been performed at the end of 4 to 6 hours, at the very latest.

CASE 10.—"A 28-year-old primigravida at thirty-nine weeks' gestation entered the hospital in early labor with a frank breech presentation. The membranes had ruptured 2 hours after the onset of labor. The cervix was completely dilated and the breech in midpelvis after 9 hours of labor . . . *no further descent of the breech occurred during the next five hours,** sterile vaginal examination was performed. It revealed firm soft tissues and a gynecoid pelvis which seemed adequate except for a contracted outlet."

Fourteen hours after the onset of labor the status of the pelvis is first discovered. The second stage of labor is permitted to continue for what must be a world's record of *13 hours.* Only then, after 13 hours of the second stage is intervention considered. This is a little too much to expect even from the wives of soldiers, or possibly the Army puts the wives through some sort of training to prepare them for such a monstrous ordeal.

Cases 6 and 8 were in labor 46 and 80 hours, respectively, before decision to operate was arrived at.

It is difficult to classify in obstetric terms or practice, the conduct of the reported labors. Radical obstetricians would have proceeded to elective section almost immediately after encountering such cases. Certainly that is the method we would have chosen. More conservative obstetricians would have allowed a 12- or 14-hour test or trial of labor only if the membranes were intact, and in the face of a ruptured sac such workers would limit their tests or trials to four to six hours.

Bourgeois' management is on no happy middle ground. It most resembles a studied neglect, a conduct of labor creating a situation in which the only choice permitted to remain possible was no choice at all; the only thing left to do was extraperitoneal section. Such management is not unheard of. We have had residents who employed similar schemes when they were trying to acquire operative experience but they limited themselves to less explosive situations. If the described conduct of labor was not aimed toward obtaining material for extraperitoneal section, how can trial or tests of labor of 19, 27, 10, 27, 17, and 38 hours be explained? How can two second stages of 13 and 9 hours be explained?

"Extraperitoneal cesarean section is steadily gaining acceptance as the procedure of choice for abdominal delivery of potentially or actually infected parturients with obstructed labor." No truer than this: that it is better to prevent potential or actual infection; that that it is better to recognize obstructed labor early; that it is better to come to a decision within reasonable and humane time limits; that in the course of practice, unforunately, there will occur the infected cases with obstructed labor to which the extraperitoneal technique will be genuinely applicable. Unfortunately, there will be no need to create material for its application.

(Signed) FRED. A. KASSEBOHM, M.D., F.A.C.S.
MILTON J. SCHREIBER, M.D., F.A.C.S.

272 WEST 90 STREET
320 CENTRAL PARK WEST

*Italics mine.

Reply by Major Bourgeois

To the Editor:

I have reviewed the communication of Drs. Kassebohm and Schreiber concerning the article, "A Peritoneal Staining Technique for Extraperitoneal Cesarean Section," which appeared in the August issue of the JOURNAL. They admit that they have no quarrel with extraperitoneal cesarean section per se, and they offer no direct criticism of the peritoneal staining technique.

The essence of their criticism is (1) that I have allowed parturients presenting a reasonable doubt as to the ultimate necessity for cesarean section to demonstrate their potentialities by a so-called test of labor, and (2) that I have electively exhibited the extraperitoneal operation.

Regarding the first point, it is germane to state that two divergent schools of thought concerning cesarean section exist. One believes that the need for section can be prophesied with certainty prior to the onset of labor. The other believes that because unpredictable factors such as distensibility of the maternal pelvic joints, molding of the fetal head, and the character of labor enter the picture, any patient presenting questionable or relative but uncomplicated disproportion deserves an opportunity to demonstrate her ability in actual labor. It has been my experience to see many such patients deliver uneventfully from below. My critics make it clear that they belong to the first school of thought; I belong to the second.

Still regarding the first point, it is generally accepted at the present time that maternal mortality following cesarean section is from five to ten times greater than maternal mortality following vaginal delivery. The incidence of maternal morbidity following section is probably greater in at least the same degree. Furthermore, effacement of the cervix and the taking up of the lower uterine segment consequent to a few hours of labor favors technical ease, and, what is even more important, the conservation of blood in any lower segment operation; these factors serve to make cesarean section safer.

Regarding the second point, I stated in the original article that two extraperitoneal cesareans had been performed electively to augment experience with the peritoneal staining technique. It was also clearly stated that the indications set forth by Drs. S. A. Cosgrove and J. F. Norton of the Margaret Hague Maternity Hospital had been followed in the other eight cases presented. Dr. E. G. Waters of the same clinic informs me (personal communication) that in approximately 300 extraperitoneal cesarean sections of his type performed by 28 operators there occurred 2 deaths. This cesarean mortality is lower than that reported for almost all comparable series of elective transperitoneal operations. Following the tenets of the three above-mentionel obstetricians I have performed cesarean section of all types 27 times in a total of 1,125 consecutive deliveries during the past thirty-one months at the AAF Regional Station Hospital, Mitchel Field, New York, a cesarean incidence of 2.4 per cent. There have been no cesarean deaths.

I leave it to the readers of this JOURNAL whether I am humane in allowing patients with relative fetopelvic disproportion a test of labor with appropriate sedation, and with the result that many doubtful cases deliver by vagina spontaneously or with the aid of simple forceps maneuver; or whether my critics, who manifestly foresee the outcome of such cases prior to labor and subject their patients to what must be a much higher cesarean incidence with its concomitant increased incidence of maternal mortality and morbidity, are more humane. The late Dr. DeLee often inquired, in effect: "How much pain is worth the life of one mother or one baby?"

The foregoing statements are my answer to Drs. Kassebohm and Schreiber from the professional point of view. Their precipitate and unfounded implications concerning Army obstetrics in general, and concerning me in particular, do not merit the dignity of a reply.

(Signed) GEORGE A. BOURGEOIS, MAJOR, M.C.
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ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Edward A. Schumann, Philadelphia, Pa. *Secretary,* Howard C. Taylor, Jr. 842 Park Ave., New York, N. Y. Annual meeting to be announced later.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* Lewis F. Smead, Toledo, Ohio. *Secretary,* James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1946.

Central Association of Obstetricians and Gynecologists. (1929) *President,* John H. Moore, Grand Forks, N. D. *Secretary-Treasurer,* W. F. Mengert, Dallas, Tex. Annual meeting Chicago, Ill., October, 1946.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President* Oren Moore, Charlotte, N. C. *Secretary,* T. J. Williams, University, Va. Annual meeting to be announced later.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Philip F. Williams, Philadelphia, Pa. *Secretary,* William Mengert, 2211 Oak Lawn Ave., Dallax Tex. Annual meeting San Francisco, July 1-7, 1946.

New York Obstetrical Society. (1863) *President,* R. A. Hurd. *Secretary,* R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* Bernard Mann. *Secretary,* John B. Montgomery, Pro tem, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* James E. Fitzgerald. *Secretary,* Herbert E. Schmitz, 25 East Washington Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* John J. Madden. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. *President,* Edward Friedman. *Secretary,* Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Charles Hunt. *Secretary-Treasurer,* Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* James S. Taylor. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. (1861) *President,* George Van S. Smith. *Secretary,* Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Roy J. Hefferman, Brookline, Mass. *Secretary,* Fred J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Goodrich C. Schauffer. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.

Washington Gynecological Society. (1933) *President,* James R. Costello. *Secretary,* Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C., Fourth Saturday, October to May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* E. L. Zander. *Secretary,* R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. (1924) *President,* S. A. Weintraub. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Albert M. Vollmer. *Secretary,* Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* T. F. Bunkley. *Secretary,* J. McIver, 714 Medical Arts Bldg., Dallas, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* Robert B. Kennedy. *Secretary,* Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Obstetric Society of Syracuse Hospitals. (1938) *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.

Alabama Association of Obstetricians and Gynecologists. *President,* J. M. Weldon, Mobile, Ala. *Secretary,* Eva F. Dodge, Montgomery, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Gerhard Ahnquist. *Secretary,* Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.

Denver Obstetrical and Gynecological Society. (1942) *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Roland S. Cron. *Secretary,* Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* R. C. Hall. *Secretary,* D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Ralph E. Leigh, Grand Forks. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* A. L. Carson, Jr. *Secretary,* L. L. Schamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.

Columbus Obstetrical and Gynecological Society. (1944) *President,* Sylvester Goodman. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held last Wednesday of each month.

Nassau Obstetrical Society. (1944) *President,* Arthur C. Martin. *Secretary,* William S. C. Dolan, 2870 Northern Blvd., Manhasset, N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Jacob Clahr. *Secretary-Treasurer,* J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* H. H. Skinner, Yakima. Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* J. Milton Singleton. *Secretary,* Richard C. Helman. Meetings, third Thursdays, September, November, January, March, and May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* George E. Judd. *Secretary,* Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Frank Locke, Winston-Salem. *Secretary,* Wallace B. Bradford, Charlotte, N. C. Meetings semiannually.